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MODELING THE SOCIAL CONTEXT OF MICROBICIDE USE

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Abstract

This paper introduces a Holistic Model of Acceptability and explores the potential of this model to identify the social context in which microbicides will likely be used once available. Data from qualitative in-depth interviews (n = 16) and quantitative surveys (n = 651) provide preliminary information. This effort represents a way to formally model likely microbicide use and is a starting point for future modeling work. A revised model for predicting microbicide use is suggested at the conclusion of the paper.

Introduction

To date, behavioral and social science research has highlighted important information on desired physical product characteristics of microbicides, how they are perceived to work, and their effects on sensation during intercourse.[2,3,4,5,6] However, far less is

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[2] Bentley ME, Fullem AM, Tolley EE, et al. Acceptability of a microbicide among women and their partners in a 4-country Phase I trial. *Am J Public Health* 94: 1159–64, 2004.
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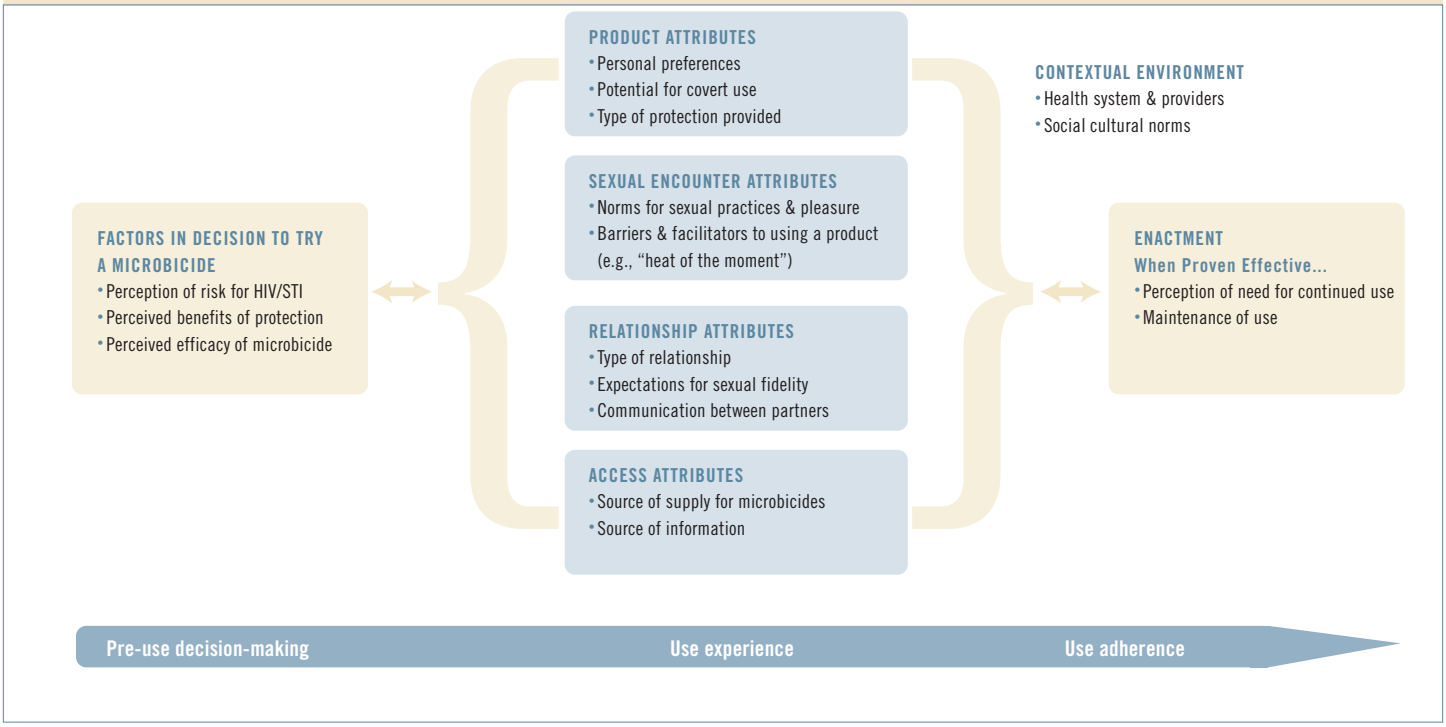
known about the social contexts in which microbicides will be used.[7,8,9] The seven-component Holistic Model of Acceptability is shown as *Figure 1*. It was adapted from a conceptual framework[10] developed to guide a US-based study of microbicide acceptability and has been subsequently adapted and used in multiple studies, guiding the generation of hypotheses and associated data collection instruments in clinical and non-clinical research.[11,12]

The model begins with *pre-use decision-making* including several *"Factors in Decision to Try a Microbicide."* Researchers[13,14] generally agree that many women and men understand how to protect themselves, yet fail to identify their own behavior as risky. The double-headed arrow between *Factors in Decision to Try a Microbicide* and the four types of attributes describing the *Use Experience* suggests that anticipation of the attributes of the product, sexual encounter, relationship, and access can also influence the decision to try a microbicide for the first time. Once a woman has identified herself to be at risk for HIV infection and has recognized that microbicides may decrease that risk, four attributes of the *Use Experience* become relevant: product attributes, sexual encounter attributes, relationship attributes, and access attributes.

FIGURE 1. HOLISTIC MODEL OF ACCEPTABILITY



[7] Koo HP, Woodsong C, Dalberth BT, Viswanathan M, Simons-Rudolph A. Context of acceptability of topical microbicides: Sexual relationships. *J Soc Issues* 61(1): 67-93, 2005.
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[12] Woodsong C, Simons-Rudolph A, Alleman P. A flexible theoretical framework for investigating acceptability in microbicide clinical trials. *Microbicides 2008*. Delhi, India, 24-27 February 2008.
[13] Bowleg L. Gender roles, power strategies, and precautionary sexual self-efficacy: Implications for black and Latina women's HIV/AIDS protective behaviors. *Sex Roles* 42(7-8): 467-780, 613-35, 2000.
[14] Darroch JE, Frost JJ. Women's interest in vaginal microbicides. *Fam Plann Perspect* 31(1): 16-23, 1999.

The *Product Attributes* box of the Holistic Model of Acceptability has three primary subcomponents. The first subcomponent, "personal preferences," includes product attributes such as ease of carrying in a purse or pocket, and the odor, color, or taste of the product as well as the product's messiness before, during, and after sex. The second subcomponent, "potential for covert use," refers to the product's ability to be used without the partner's knowledge. The final subcomponent, "type of protection provided," represents the microbicide's effectiveness in preventing HIV, sexually transmitted infections (STIs), and/or pregnancy. Some women will be interested in protection from all three, while others may consider the contraceptive potential of some products to be a negative attribute.

The *Sexual Encounter Attributes* include the subcomponents "norms for sexual practices and pleasure" and "barriers and facilitators to using a product." There is great variation in what is considered pleasurable during sex and the values attached to sexual satisfaction and physical intimacy. However, there is only scant information about how these norms relate to microbicide acceptability. "Barriers and facilitators to using a product," the second *Sexual Encounter Attribute*, refers to such characteristics as the timing of use relative to the sex act and duration of protective effect or "heat of the moment."

Although women cannot always dictate the terms of their own sexual relationships, some women in high-risk relationships are able to take steps to protect themselves from HIV. The *Relationship Attributes* posited to affect microbicide use include the "type of relationship." For example, women in more casual and/or less monogamous relationships may be more likely to use microbicides than women in more stable and/or more monogamous relationships. In addition, "expectations for sexual fidelity" can affect microbicide use if use implies that one partner has violated this expectation. For example, if a woman initiates microbicide use in an ongoing steady sexual relationship, this may suggest that she doubts her partner's faithfulness, or that she herself has been unfaithful. The final component of the *Relationship Attributes*, "communication between partners," considers whether sexual partners discuss HIV risk and risk reduction strategies.

The final *Use Experience* component, *Access Attributes*, includes the source of both the supply of microbicides and information about them. Access to and availability of microbicides at public health facilities, over the counter, or by prescription may be important determinants of use, especially when compared with condoms, which are relatively inexpensive, widely available, and recommended by health professionals. Some advocates[15] suggest that how women learn about the technology is as important to long-term use as product characteristics themselves. We believe that various sources of information will be important, including health professionals' recommendations as well as those of relatives, friends, and acquaintances.

Use Adherence refers to correct and consistent use of a microbicide over time. Although *Use Adherence* is impossible to measure at this stage in microbicide development, we suggest measures that would indicate sustained correct and consistent use once proven-effective microbicides are available. These include "perception of need for continued use" and "maintenance of use." Logically, the *Use Experience* attributes influence whether microbicide use will continue beyond the initial use experience. However, the double-headed arrow between *Use Experience* and *Use Adherence* suggests that continued use of a microbicide may also influence how the participant later understands the *Use Experience* attributes.

An overarching consideration for the model is the larger contextual environment. The health care system, provider influences, and social and cultural norms influence each component of the model.

Methods

The study, *Acceptability of Microbicides Across Risk Groups and Time*, used a

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[15] Center for Women Policy Studies. Building a national policy agenda: Ten principles for woman-focused HIV/AIDS prevention, 1996.

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mixed-method design to explore domains of microbicide acceptability among US women and men, with an initial phase of qualitative data collection followed by a quantitative phase. This paper uses a subset of data from this study. This subset includes 16 in-depth interviews with women aged 18 or older and 651 quantitative surveys of women aged 16-45 collected primarily from family planning and sexually transmitted disease clinics in a large public health department in North Carolina, USA. Eligibility criteria included: women aged 16 or above, self-identified as heterosexual, sexually active (averaging at least one episode of vaginal intercourse with a male per week), not currently pregnant, not less than four weeks post-partum, not self-identified as HIV-positive, no previous negative reactions to vaginal products, and no current or previous participation in another study involving vaginal products. Participants for both phases of the study were selected from the same recruitment venues, using the same eligibility criteria.

The Holistic Model of Acceptability served as a conceptual framework guiding development of data collection instruments for the study. It was modified iteratively during both the qualitative and quantitative phases.[16] Qualitative in-depth interviews were collected from January 2001 to May 2002. Audio recordings of these interviews were transcribed and coded using NVIVO 2.0 software; an 85% intercoder agreement was maintained between the coders.

Quantitative data from baseline and follow-up surveys were collected from March 2003 to March 2004. At the end of the baseline survey interview, respondents were randomly assigned one of two forms of vaginal lubricants (as proxies for microbicides)—either a suppository or a gel[17]—and asked to use their lubricant during sexual intercourse before they returned for a follow-up interview (on average, 33 days later), to report on their experiences using the product and other issues. Only participants responding to both baseline and follow-up surveys in the quantitative phase of the larger study were included in the quantitative analysis reported here. The baseline survey provided data for variables in the pre-use decision-making and use experience portions of the model (prior to use of the proxy product), and the follow-up survey captured the outcome of interest. Variables representing each model construct are listed in *Table 1*. In most cases, model constructs are represented by variables based on single questionnaire items. Many of the items came from two sets of questions. One set asked "how important is it to you that a vaginal protection product" had each given feature from a list of features, with responses "extremely important," "very important," "somewhat important," "not important," and "don't know." The first two responses were grouped to represent "important." "Somewhat important" and "not important" were grouped to represent "not important;" and "don't know" was set as a missing response. Another set of questions asked "how willing you would be to use a product" that had each given feature. Responses "very willing" and "somewhat willing" were grouped to represent "willing;" and responses "not at all willing" and "don't know" were grouped to be "not willing." All variables, whether based on single or multiple questions, were coded as dichotomous variables.

Five constructs are based on variables drawing upon multiple questionnaire items. A woman's responses to the multiple items representing each construct were added together and set to "1" if the sum fell in the upper half of the resulting scale, and "0" in the lower half. For example, the survey asked "how important is it to you that a vaginal protection product" "is effective against HIV/AIDS," "is effective against STDs," and "is effective against pregnancy." For each question, the four response categories ranging from "extremely important" to "not important" were assigned values of 4 to 1, respectively. A respondent's responses to the three questions were summed, and coded as "1" if it was higher than the mid-point (7.5 in this case), and "0" otherwise. Other response-category composite variables were created in a similar fashion.

The outcome variable, "likely enactment," is based on the respondent's choice of answers in the follow-up survey to a question asking how likely she was to try

[16] For more detail on study design, please see reference #7 and Simons-Rudolph A. The social context of microbicides: Exploring the reality of a covert, woman-controlled HIV-prevention method. In: *Public Policy Dissertations*. The George Washington University: Washington, DC. 2007.

[17] Participants were told that the proxy product did not protect against HIV, other STIs, or pregnancy and explicitly signaled their understanding of this in writing during the informed consent process. The proxy products given, Replens® and Lubrin® brand lubricants are widely available over the counter and have been evaluated for safety by the US Food and Drug Administration. At the time this study was conducted, microbicides were not available for study and thus we used proxies for microbicides to investigate acceptability.

a new vaginal protection product given the following conditions that were stated to her: she was beginning a new relationship; she wanted to protect herself against STDs, HIV, and pregnancy; the "new vaginal protection product" was safe, easy to get, cost the same as a condom, and she did not have to interrupt sex to use it; and it was "half as effective as condoms" but protects only her and not her partner.[18] A respondent was deemed likely to enact if she chose either "very likely" or "somewhat likely" to try the described new vaginal protection product; she was coded as not likely to enact if she chose "not at all likely."

The relationships between the independent variables representing the constructs in the model and the enactment variable were tested for significance using 2x2 chi square tests. The univariate and bivariate analyses were conducted using SAS® 9.1.

Results

The in-depth interview respondents included seven African-American, six Hispanic, and three Caucasian adult women aged 18 and older (no further demographic data were collected from the qualitative participants). Quantitative participants were generally young, unmarried, black or Latina, and reported that they were struggling financially. Women were 16-45 years old, with a mean age of 27.5; most (70.8%) were younger than 31. Most participants (69.7%) were not married at the time of the study. More than three-quarters of survey respondents self-identified as either African-American (57.9%) or Latina (25.0%). About half (50.5%) reported difficulty paying their rent, mortgage, telephone, electric, or gas bills in the previous 12 months. Quantitative respondents reported a range of 1-5 sexual partners in the previous 12 months with a mean of 1.6 partners (sd=0.9). Data presented below summarize findings primarily from the quantitative data, with information from the qualitative in-depth interviews providing further illustration.

Factors in decision to try a microbicide

Table 1 (see p. 6) presents univariate statistics of each component of the Holistic Model of Acceptability based on data from the baseline survey. Overwhelmingly, respondents (92.5%) considered getting AIDS to be serious and 34.6% identified themselves as having a 50/50 chance of getting HIV. The qualitative findings also suggest that a respondent's decision to use a microbicide would be impacted by her own perception of HIV and labeling of her current sexual relationship as risky. Monogamous respondents reported that they would not use a product in a relationship because it would arouse mistrust. As one African-American woman stated, "Married people don't use [HIV/STI] protection." Respondents indicated that having and/or using a microbicide would suggest either that the woman was cheating or that she thought her partner was unfaithful. In fact, this was the most frequently cited perceived risk of microbicide use in the in-depth interviews. Qualitative participants also noted that product use could circumvent the need for difficult conversations about HIV risk. This was perceived to be a key benefit of microbicide use.

Product attributes

Product attributes such as color, odor, taste, messiness, and ease of carrying were important to most (85.8%) respondents. Approximately half (55.2%) of baseline respondents were willing to touch their own vagina with their fingers or an applicator to insert the product. Overwhelmingly (97.7%), quantitative respondents want a microbicide that would be effective against HIV, STIs, and pregnancy. Most respondents (81.0%) also wanted a microbicide that could be used covertly ("without your partner knowing"). In addition, the in-depth interviews indicated that the "naturalness" of the product was central to its acceptability. One qualitative respondent said that "women are looking for that natural feeling" of unprotected sex when considering an HIV prevention product. Women wanted a product that would not be noticed in part because they did not want to raise the issue of trust and sexual

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[18] Although the survey asked about three other scenarios varying the level of effectiveness and partner protection, this scenario is expected to be closest to a first-generation microbicide and is the only one examined in the present paper. That is, the first microbicides are not likely to exceed 60% efficacy and partner protection is not being tested in many current clinical trials.

TABLE 1. DESCRIPTIVE STATISTICS (n = 651)

	# of variables used in each construct	Response categories coded as 1[19]	% (n) coded as 1
Independent Variables[20]			
FACTORS IN DECISION TO TRY MICROBICIDE FIRST TIME			
Perception of risk for HIV/STI (Chances of getting HIV or AIDS)	1	A "very strong chance," a "strong chance," "some chance 50/50"	34.6 (225)
Perceived benefits of protection "With the medicines available today, it's not a big deal to get AIDS"	1	Disagree "completely" or "somewhat"	92.5 (602)
Perceived efficacy of microbicide	Stated in question eliciting likely enactment as "half as effective as condoms" and "protects only you and not your partner"		
PRODUCT ATTRIBUTES			
Personal preferences (Importance that product is easy to carry in a purse or pocket, has no noticeable odor, is clear in color, does not have a noticeable taste, and is not messy)	5 (1 for each preference)	Composite: "extremely" or "very" important	85.8 (558)
Other personal preferences (Willingness to touch vagina or use an applicator to insert product)	2 (1 for finger, 1 for applicator)	Composite: "very" or "somewhat" willing	55.2 (358)
Potential for covert use (Importance of "can be used without your partner knowing")	1	"Extremely" or "very" important	81.0 (527)
Type of protection provided (Importance of effectiveness against HIV/AIDS, STDs, and pregnancy)	3 (1 each on HIV, STI, and pregnancy)	Composite: "extremely" or "very" important	97.7 (636)
SEXUAL ENCOUNTER ATTRIBUTES			
Norms for sexual practices and pleasure (Willingness to use a product that "made the vagina feel wetter than usual during sex" and if "should not douche for about 6 hours after use")	2 (1 for vaginal wetness, 1 for douche)	Composite: "very" or "somewhat" willing	73.0 (472)
Norms for sexual practices and pleasure (Willingness to use a product that decreased sexual pleasure for either partner)	1	"Very" or "somewhat" willing	35.3 (229)
Barriers & facilitators to use a product in the "heat of the moment" (Willingness to use if "had to wait 15 minutes before you can have sex" after insertion)	1	"Very" or "somewhat" willing	83.8 (544)
RELATIONSHIP ATTRIBUTES			
Type of relationship	Only analyzed qualitatively		
Expectations for sexual fidelity (In the past 12 months, how many different men have you had voluntary vaginal sex with?)	1	2 or more sexual partners	34.4 (224)

TABLE 1. DESCRIPTIVE STATISTICS (n = 651) *Continued*

	# of variables used in each construct	Response categories coded as 1[19]	% (n) coded as 1
Communication between partners[21] (During your entire relationship, (did you ever talk/have you ever talked) with (main partner/ other sexual partner) about: -using protection against STDs or HIV -his sexual history-for example, how many people he has had sex with -whether he's had STDs or HIV?)	3 items each for up to 2 partners per respondent ("relationship partner" and "non-relationship/sex-once partner")	Composite: Yes, did talk about these	84.3 (549)
ACCESS ATTRIBUTES			
Source of supply (Importance of whether the product is easy to get)	1	"Extremely" or "very" important	90.5 (589)
Source of information (Importance of recommendation from respondent's doctor or other health care provider)	1	"Extremely" or "very" important	83.3 (542)
Source of information (Importance of product being used by friends, relatives, and acquaintances)	1	"Extremely" or "very" important	38.3 (248)
Dependent Variable[22]			
Likely Enactment (How likely respondent would use new vaginal protection product under the stated conditions[23])	1	"Very" or "somewhat" likely	62.7 (408)

[19] The remaining categories were coded "0," i.e., less chance (not much chance, no chance at all) for perception of risk; agreed (somewhat or completely) for perceived benefit; "not important" for all "important" variables; "not willing" for "willing" variables; "one partner" for expectations for sexual fidelity; "no" did not talk for communication between partners.

[20] Taken from baseline data before use of the proxy product.

[21] Communication between respondent and "relationship partner" and (if applicable) between respondent and "non-relationship/sex-once" partner.

[22] Taken from follow-up data after proxy product use.

[23] Under the stated conditions that she was beginning a new relationship and wanted to protect herself from STDs, HIV, and pregnancy; that the microbicide was safe, easy to get, costs the same as a condom, and she did not have to interrupt sex to use it; and it is half as effective as a condom and protects only the woman and not her partner.

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fidelity with their partners. A product that feels "natural" may not be detected and thus need not be discussed with a sexual partner.

Sexual encounter attributes

In terms of a microbicide's impact on the sex act itself, almost three-quarters (73.0%) of respondents were willing to use a product that affected vaginal wetness or whether they could douche immediately after sex. Few (35.3%) were willing to use microbicides if it diminished sexual pleasure. Most women (83.8%) believed that they would be willing to use a microbicide in the "heat of the moment" (i.e., if they had to wait 15 minutes to have sex after inserting the product). Qualitative respondents also expressed confidence in their ability to use a product in the "heat of the moment." Many qualitative respondents could not imagine a situation in which they would not be

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able to protect themselves from HIV. This was equally true of Caucasian, African-American, and Hispanic women. As one woman told us, "If they had something like that [a product that would protect a woman from HIV and met her personal preferences] I would definitely use it, regardless of the circumstances. When we first started using [the proxy product], it was a distraction having to wait, but if there was something like [the proxy product], I would use it."

Relationship attributes

The quality and social context of sexual relationships provide an important lens through which these data are understood. Quantitative respondents reported an average of 1.6 partners in the past 12 months, and most (84.3%) reported discussing the three issues regarding HIV risk with their partners in the previous 12 months. Qualitative respondents reported discussing risks regardless of relationship status. Although no qualitative respondents reported themselves to be immune from HIV risk, they reported that this risk differs by relationship type. Qualitative respondents perceived that it is both more acceptable for women in casual relationships[24] to protect themselves without needing to negotiate HIV protection with their partners, and they would be more likely to do so. The nature and timing of communication about risk and risk reduction strategies also vary by the type of relationship. When speaking of a recent steady relationship, one African-American woman told us, "Yes, at that time I [would have] told him when I was about to get [the product]. If I was more comfortable [in a stable relationship], I would have brought it up ahead of time. If I was less comfortable [in a less stable relationship], I would have explained it afterwards because he obviously would see me doing it."

For qualitative respondents, discussing STIs was generally more difficult than discussing pregnancy prevention. Talking about STIs was generally seen as taboo and uncomfortable, and respondents reported discussing HIV prevention after conversations about unintended pregnancy prevention.

Access attributes

Availability and cost information for microbicides is not yet known. Almost all respondents (90.5%) wanted easy access to a microbicide, and qualitative respondents reported that the microbicide cost should be comparable to that of condoms (approximately US$1.00 per application).

Once proven-effective microbicides are available, our data indicate that health care providers and social networks may be effective means of promoting microbicides. Most (83.3%) survey respondents reported that a health care provider's recommendation of a microbicide was important to them, whereas 38.3% of respondents answered the same with respect to relatives, friends, and acquaintances. Although most qualitative respondents mentioned that they would not use a product that their doctor disliked, none reported that their decision to use a microbicide would be based solely on a recommendation from a health care provider. In particular, African-American and Hispanic qualitative respondents emphasized the importance of peers and media advertising to normalize microbicide use for them and their friends. An African-American woman told us, "If a whole bunch of people my age use it, [the microbicide] would have to be something I was familiar with or something that was advertised a lot. I would have to know people who used it." The qualitative data also suggest that negative perceptions from health care providers are much more salient than a generally positive recommendation. Few qualitative respondents said that they would use a product that their doctor told them was dangerous or otherwise unacceptable.

(Likely) enactment

More than three-fifths of respondents (62.7%) reported in the follow-up survey that they were likely to use a microbicide *(see Table 1)*. Since most of them reported that they had used the proxy products during sexual intercourse, these responses were informed by their experience with the proxy products given to them at baseline. As seen in *Table 2*, of the 13 independent variables in the model, five were significantly ($p < .05$) related to "likely enactment." These variables were "perceived benefits of protection," "personal preferences/willingness to touch vagina," "norms for sexual practices and pleasure/increased vagina wetness/no douche 6 hours," "norms for sexual practices and pleasure/decreases sexual pleasure for partner," and "barriers and

[24] Defined by respondents as "one night stands," "not serious," and otherwise not emotionally or legally committed.

TABLE 2. VARIABLES FROM HOLISTIC MODEL OF ACCEPTABILITY AS PREDICTORS OF LIKELY ENACTMENT (n = 651)

	% (n) likely to use a microbicide once available[25]	P-value[26]
Perception of risk for HIV/STI		0.325
At risk: Perceive at least 50/50 chance of contracting HIV	65.3 (147)	
Not at risk: Perceive less than 50/50 chance of contracting HIV	61.4 (261)	
Perceived benefits of protection (with the medicines available today, it's not a big deal to get AIDS)		0.025*
Agree-Not a big deal	61.5 (370)	
Disagree-Is a big deal	77.6 (38)	
Personal preferences (odor, color, taste, messiness, ease of carry)		0.086
Important	61.3 (342)	
Not important	70.7 (65)	
Personal preferences (willingness to touch vagina to insert product)		0.002**
Willing	67.9 (243)	
Not willing	56.2 (163)	
Potential for covert use (can be used "without partner knowing")		0.724
Important	63.0 (332)	
Not important	61.3 (76)	
Type of protection provided (important to protect from HIV, STI, pregnancy)		0.160
Important	62.3 (396)	
Not important	80.0 (12)	
Norms for sexual practices & pleasure (willingness to use product if respondent had increased vaginal wetness during sex, and could not douche for up to 6 hours after sex)		0.008**
Willing	65.7 (310)	
Not willing	54.3 (95)	
Norms for sexual practices & pleasure (willingness to use product if it decreased sexual pleasure for respondent or partner)		0.004**
Willing	70.3 (161)	
Not willing	58.7 (246)	
Barriers & facilitators to use a product in the "heat of the moment" (willingness to use product if respondent had to wait 15 minutes to have sex after product insertion)		0.030*
Willing	64.5 (351)	
Not willing	53.3 (56)	
Expectations for sexual fidelity (willingness to use product if had X partners in the past 12 months)		0.338
2 or more partners	65.2 (146)	
1 partner	61.4 (262)	
Communication between respondent and "relationship partner" and (if applicable) between respondent and "non-relationship/sex-once" partner (whether respondent discussed using protection against STDs or HIV, his sexual history, and whether he's had an STD or HIV)		0.811
Yes	62.5 (343)	
No	63.7 (65)	

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TABLE 2. VARIABLES FROM HOLISTIC MODEL OF ACCEPTABILITY AS PREDICTORS OF LIKELY ENACTMENT (n = 651) *(Continued)*

	% (n) likely to use a microbicide once available[25]	P-value[26]
Source of supply (willingness to use if product is easy to get)		0.554
Important	62.3 (367)	
Not important	66.1 (41)	
Source of information (recommendation by doctor or health care provider)		0.059
Important	61.1 (331)	
Not important	70.6 (77)	
Source of information (is used by relatives, friends, and acquaintances)		0.076
Important	66.9 (166)	
Not important	60.0 (240)	

[25] Under the stated conditions that she was beginning a new relationship and wanted to protect herself from STDs, HIV, and pregnancy; that the microbicide was safe, easy to get, costs the same as a condom, and she did not have to interrupt sex to use it; and it is half as effective as a condom and protects only the woman and not her partner.

[26] P-value from 2 x 2 chi square tests of significance; * $p < .05$; ** $p < .01$

facilitators to using a product/heat of the moment" *(see Table 2)*. These variables represent items within all constructs in the Holistic Model of Acceptability with the exception of relationship and access attributes. In addition, the relationships of three variables were near significance ($p < .10$), including preferences regarding odor, color, etc., recommendation by health care provider, and use by relatives and friends.

Discussion

This paper delineates one possible way to model the social context in which microbicides will likely be adopted. Although some of the measures were only approximate indicators of the desired constructs, and some were not significant predictors of likely enactment, the multi-method data in this study identify some aspects of microbicide acceptability that are likely important determinants of use. Since the Holistic Model of Acceptability is a potential starting point for future modeling work, we make some suggestions for improvement that reflect our initial findings. A revised model named Microbicide Use Model is shown in *Figure 2 (see p.11)*.

As some preferences seem to be more salient than others, a hierarchical "decision-making tree" may be better suited to model likely microbicide use. The results here suggest that some aspects of use are more salient. For example, "perceived benefits of protection" (i.e., "will microbicide protect me") and the desire for product as a "natural" lubricant/sex enhancer came out strongly in the quantitative and qualitative analyses, respectively. Other characteristics such as *Product Attributes* (especially odor, color, taste, messiness, and ease of carrying) were not as salient and thus are placed later in the model. The placement of these *Product Attributes* in the Microbicide Use Model reflects the possibility that the perception of product characteristics is filtered through relationship variables such as "expectation of trust in a relationship." Of note, the Microbicide Use Model highlights the importance of perception of risk for HIV. Researchers worry that effective prevention techniques as well as AIDS treatment may change the perception of risk and lead to riskier sexual behaviors.[27,28] However, the alternate path shown in the Microbicide Use Model allows for the possibility that a woman unconvinced of its efficacy may use a microbicide as a sex enhancer (for example) and thereby increase her own protection. It is our hope that the Microbicide Use Model clarifies some of the central aspects of microbicide acceptability and presents a more straightforward way to evaluate and revise understanding within the field

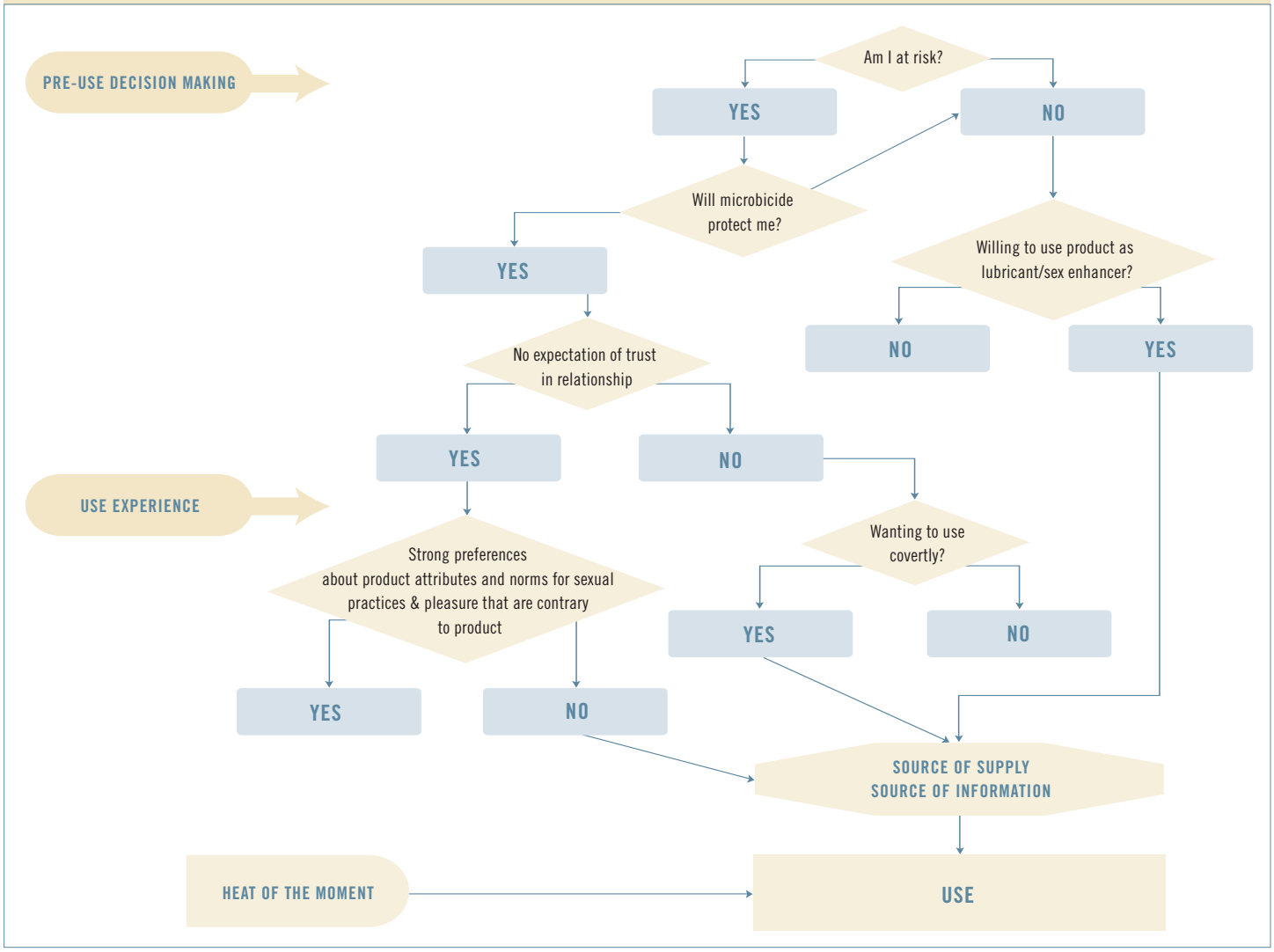
[27] Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: The achilles' heel of innovations in HIV prevention? *BMJ* (332): 605-7, 2006.

[28] Leeder S. Risky business. *Australian Doctor*, 2005.

as more data and more precise measures become available.

This study should be interpreted with caution. It includes data from a narrow sample of US women, and thus generalizability is limited. Another limitation relates to the lack of independence of the model from the data. The model grew organically and we consider it to be one that is flexible as new literature emerges. The Holistic Model of Acceptability and the revised Microbicide Use Model present initial ways to think about modeling microbicide use. Microbicides present the best HIV prevention hope for millions of women, and we must continue to better understand who, when, and with whom women are likely to use a microbicide.

FIGURE 2. MICROBICIDE USE MODEL



MICROBICIDES IN CHINA

Alan Stone (MEDSA Limited, London, United Kingdom) and Tim Farley (Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland)

The Chinese Ministry of Health and UNAIDS estimate that as of October 2007, 700,000 HIV infections have occurred in China. While this translates to a low prevalence given that country's population of more than 1.3 billion, the incidence of new infections is increasing and the routes of transmission are shifting.[1] In the mid-1980s the affected population comprised predominantly injecting drug users (IDUs), particularly in areas of Yunnan Province bordering the heroin-producing "Golden Triangle" regions of Myanmar, Laos, and Viet Nam. A second focus of infection occurred in Henan Province among blood and plasma donors through the use of contaminated equipment. From these two foci, the virus has spread throughout China. During 2007, there were 7,000 new HIV infections, a 30% increase on the previous year's estimate. Almost 50% of these were acquired through sexual contact and the proportion of women infected is rising dramatically.

In recognition of these trends, there is growing interest in microbicides as an important additional element of HIV prevention. One focus of microbicide-related research in China has been on various surfactant preparations and products such as silver ions and povidone iodine. Indeed, some preparations containing these products are currently on the market and are being promoted as "microbicide/spermicide for preventing unwanted pregnancy and protecting against infection with HIV and other STIs," even though clinical trials to demonstrate their safety and effectiveness have never been undertaken.[2] This undesirable situation, together with growing awareness of the need to develop effective interventions, has led over the past four years to informal discussions about microbicides with Chinese scientists, government officials, and representatives from the pharmaceutical industry. These talks have confirmed that closer collaboration between the microbicide development community in China and microbicide scientists in other countries would be warmly welcomed. In order to encourage such collaboration, the WHO Department of Reproductive Health and Research, USAID, and Nanjing University sponsored a three-day symposium on "Scientific, Regulatory, and Public Health Aspects of Microbicide Research and Development." This meeting was held in Nanjing on 3-6 November 2008, and was attended by 139 delegates, of whom 18 were scientists from Europe, India, South Africa, Thailand, and the United States (USA).

The symposium was designed so that it would be valuable to a wide range of delegates, including those relatively new to the field as well as to experts. It covered all components of the microbicide enterprise, from discovery and preclinical and clinical evaluation to regulation, industrialization, and marketing.

Note: In the pages which follow, the names of Chinese colleagues are written in the conventional Chinese way, i.e., family name first, followed by the given name.

Features of the Epidemic

The meeting opened with a review of the main characteristics of the HIV/AIDS epidemic so as to ensure that all present were aware of the nature and scale of the problem that microbicides are intended to combat. *Kim Dickson (WHO Department of HIV/AIDS, Geneva, Switzerland)* summarized some of the all-too-familiar but nevertheless grim global statistics: 33 million people living with HIV in 2007, 50% of them women and, in that year, 2.7 million new HIV infections and 2 million AIDS-related deaths. She referred to the political initiatives taken by WHO, the United Nations, and G8[3] and spoke about the available spectrum of interventions aimed at controlling the spread of the virus. Those included interventions already being implemented, such as safer-sex education, needle-exchange programs, condom promotion, prevention of mother-to-child transmission (PMTCT) of HIV with antiretrovirals (ARVs), and male circumcision, and those under development, including vaccines, cervical barriers, oral pre-exposure prophylaxis (PrEP) and, of course, microbicides.

[1] Lu L, Jia M, Ma Y, et al. The changing face of HIV in China. *Nature* 455: 609-11, 2008.
[2] Jiang S, Liu S, Stone A. China needs safe and effective microbicides for preventing sexual transmission of HIV. *Lancet Infect Dis* 6: 681-2, 2006.
[3] Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States.

Zhang Linqi (Comprehensive AIDS Research Center, Tsinghua University, Beijing, China) and *Wang Ning (National Center for AIDS Control and Prevention, Chinese CDC)* reviewed aspects of the HIV/AIDS epidemic in China. The main foci of infection have been mainly in rural areas in Yunnan and Henan provinces *(see above)*, but the epidemic is now shifting to urban communities, with most infections occurring in the economically productive age range of 20-50. In Yunnan, the most severely affected province, the virus is spreading from the high-risk IDUs to the general population through heterosexual activity. The virus is also taking hold in men having sex with men (MSM).

Some features of the epidemic in India were discussed by *Badri Saxena (Centre for Policy Research, New Delhi, India)*. Revised estimates based on sentinel surveys and a population-based National Family Health Survey indicate that India is home to 2.5 million infected people, with prevalence among adults of 0.36% and sexual transmission accounting for 86% of infections. The dynamics of the epidemic are shifting from high-risk groups to the general population, from high-prevalence states to all states, from urban to rural settings (the latter being the converse of the major trend in China), and display increasing feminization.

Wang Baoxi (Director, National Center for STD Control, Chinese CDC, Beijing, China) presented data on the alarming resurgence of syphilis in China, particularly in female sex workers and MSM (prevalence about 14% in each group). Co-infection with HIV is common. The Government has allocated a special budget for tackling this problem and has developed national guidelines for syphilis surveillance, screening, and treatment, and plans for a comprehensive sexually transmitted infection (STI) control program. The Government's provisions for HIV-infected people, including access to antiretroviral treatment (ART), were described by *Zhang Fujie (National Center for AIDS/STD Prevention, Chinese CDC, Beijing, China)*, who referred to the infrastructural inadequacies which the program will have to face. An ongoing pilot study is exploring the integration of family planning with HIV/STI control, including condom distribution.

The Significance of Microbicides

In order to set the scene for the more detailed discussions to follow, the basics of microbicide science and the role of microbicides in the context of other prevention strategies were described by *Alan Stone [MEDSA Ltd, London, United Kingdom (UK)] and Judy Manning (USAID, Washington, DC, USA).* The point was made that while most microbicide research in China is focused on discovery and preclinical studies, the identification of a novel microbicide candidate, for example, through screening traditional medicinal products, is only the beginning of the development process. Even if a new substance is shown to be a potent inhibitor of a range of HIV strains *in vitro*, complex issues such as toxicity, formulation, stability, mucosal distribution, and pharmacokinetics would still have to be addressed, with safety being a matter of paramount importance.

The question of what impact microbicides might have on the public health of countries with severe HIV/AIDS epidemics was addressed by *Tim Farley (Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland)*, who presented some of the conclusions reached by *Charlotte Watts, et al. (London School of Hygiene and Tropical Medicine, London, UK)* based on mathematical modeling. No modeling of this kind has yet been carried out in the China context.

Henry Gabelnick (CONRAD, Arlington, VA, USA) brought the meeting up to date on microbicide clinical trials. He summarized the ongoing effectiveness trials of PRO 2000 and BufferGel® and clinical studies on the safety and acceptability of VivaGel®, tenofovir, and dapivirine. The disappointing outcomes of the recently completed trials of Carraguard® and cellulose sulfate (Ushercell) provided salutary examples of products which appeared to perform well in extensive laboratory tests of safety and efficacy, yet did not prove to protect people against infection with HIV, gonorrhea, or chlamydia. It is not yet known why these results diverged from expectations based on preclinical studies.

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MICROBICIDES IN CHINA *(Continued from p.13)*

Nevertheless, despite these setbacks, a great deal has been learned from these trials to help guide the choice of future candidates and the methodology of future effectiveness studies.

The session was concluded by a presentation by *Wu Allen Zhiwei (Center for Public Health Research, Nanjing University, Nanjing, China)* about some of the microbicide candidates under development in China. Technologies available in China relevant to this work include cell- and tissue-based *in vitro* systems, non-human primates, and small animal models. Nifeviroc, developed by researchers at institutes of the Chinese Academy of Sciences in Shanghai, is a small-molecule fusion inhibitor which binds strongly to CCR5 (not to CXCR4) at nanomolar concentrations. It is said to be as potent an inhibitor of HIV as Fuzeon®, a fusion inhibitor developed and marketed by Trimeris and Hoffmann-La Roche. It is active against a wide range of genetic subtypes and drug-resistant strains, including one that is multi-resistant to several of the reverse transcriptas inhibitors and protease inhibitors currently employed in clinical treatment. Chongqing Frontier Biotechnology Company has developed a peptide, FB006, which targets a highly conserved region of gp41. This too inhibits a wide range of HIV strains including R5, X4, and multi-drug-resistant strains. Other researchers are working on various agents, including sulfated bacterial glycans and theaflavin derivatives, which are thought to prevent virus-cell attachment/fusion by non-specific means. Work is also proceeding on several thermoreversible gels capable of extended residence in the vagina, one being developed as a contraceptive, one based on low pH, and one containing mono-aldehyde gossypol.

Discovery, Lead Development, and Non-Clinical Assessment of Safety and Efficacy

Jiang Shibo (New York Blood Center, New York, NY, USA) explained how the discovery of the potent HIV entry inhibitor cellulose acetate 1,2–benzenedicarboxylate (cellacefate/CAP) had resulted from the screening of more than 200 pharmaceutical excipients. While CAP slowly hydrolyzes in aqueous media, it remains stable when formulated as a rapidly dispersible dry tablet. *In vitro* studies have shown that the combination of CAP with the non-nucleoside reverse transcriptase inhibitor (NNRTI) MIV-160 is strongly synergistic and inhibits a range of HIV strains resistant to reverse transcriptase (RT) inhibitors. *In vitro* systems incorporating human genital epithelia and their value in assessing microbicide potency and toxicity were described by *Olivier Delezay (University Jean Monnet, St. Etienne, France).* Referring to the fact that the majority of laboratory studies have been carried out with free HIV particles, he raised the often-overlooked issue of the relative importance of various viral forms in the semen of HIV-infected men: cell-associated virus, free virus particles, and opsonized virus. He drew attention to the related question of the role of semen components in modulating inflammation of the female genital tract and the influence of such effects on infection.

Cecilia Cheng-Mayer (Aaron Diamond AIDS Research Center, New York, NY, USA) considered the uses and limitations of non-human primate (NHP) models in assessing microbicide safety and efficacy, and compared the pros and cons of a repeat low-dose challenge approach against those of a single high-dose challenge following Depo-Provera treatment. She described the use of these models in evaluating the protective capability of CAP, zinc finger inhibitors, cellulose sulfate, and lactobacilli engineered to express the fusion inhibitor T45. Her talk concluded with a caution about the predictive value of the NHP model, which will only be clear once there are effectiveness data from human trials. *Chen Zhiwei (AIDS Institute, University of Hong Kong, Special Administration Region of China)* explained that his institution has facilities for NHP studies of vaccines and microbicides. His team has generated CCR5-tropic chimeric simian-human immunodeficiency viruses (SHIVs) based on two of the predominant HIV types circulating in China.

Several microbicide candidates derived from natural products were described by *Liu Shuwen (Southern Medical University, Guangzhou, China).* Anhydride-modified beta-lactoglobulin (B69) and other

similarly modified proteins inhibit HIV replication by blocking the gp41-CD4 interaction. B69 is also active against herpes simplex virus (HSV) and chlamydia, is inexpensive, and is stable in aqueous media. Work on the spermicidal surfactant deoxycholyltyrosine as a potential microbicide is reminiscent of similar work on deoxycholate derivatives in the United Kingdom that was terminated in the early 1990s. *Xu Qiang (Osel Incorporated, Santa Clara, CA, USA)* reported on progress with *Lactobacillus jensenii* engineered to express a modified cyanovirin. These bacteria can persistently colonize the vaginas of Chinese rhesus macaques and express the active agent. If required, they can be cleared from the vagina by inserting an azithromycin suppository. He explained that while these are encouraging results, several issues arise in the context of applicability to humans, including the relative fitness of the engineered organisms in comparison with their natural counterparts and the question of cultural acceptability in different communities. Studies on the use of novel vesicles based on tetra-ether lipids as a means of delivering molecules to mucosal surfaces were described by *Xu Yuhong (Shanghai Jiaotong University, Shanghai, China).*

Clinical Development

Henry Gabelnick (CONRAD, Arlington, VA, USA) outlined the essentials of Phase 1, 2, 2B, and 3 clinical trials of microbicides, pharmacokinetic assessments, and male tolerance studies. He made it clear that, in the light of recent experience, the clinical safety endpoints currently measured need to be complemented by new ones capable of better detecting effects that might enhance the risk of HIV infection, such as inflammatory responses, inhibition of innate defense mechanisms, epithelial disruption, and adverse effects on the resident microflora.

Tim Farley (Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland) explained the role of the Data and Safety Monitoring Board (DSMB) and its responsibility for making recommendations to trial sponsors on trial continuation; termination for evidence of benefit, harm, or futility; and/or the modification of procedures to minimize risks.

A report on the status of preclinical and clinical research on ARV-containing microbicides was presented by *Salim Abdool Karim (University of KwaZulu-Natal, Durban, South Africa)*. Following successful macaque-challenge studies with tenofovir gel and subsequent Phase 1 and 2 trials and male tolerance studies, the CAPRISA Phase 2B proof-of-concept trial was launched in 2007, with results anticipated in early 2010. He described the Microbicide Trials Network's (MTN) VOICE study, due to start enrolling participants in mid-2009, in which tenofovir gel will be compared with oral tablets containing either Viread® (tenofovir disoproxil fumarate) or Truvada™ [Viread® plus the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine]. The status of work on microbicides based on the NNRTIs dapivirine (TMC120), UC-781, and MIV-150 and on the CCR5 blocker maraviroc was also discussed, as well as research on various potential combinations of these and other candidate microbicide compounds.

Lynn Paxton [US Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA] reviewed some of the main challenges confronting large-scale microbicide trials and went on to explain how the International Partnership for Microbicide's (IPM) adaptive trial design might overcome some of them. The first stage of such a trial would involve multiple candidates and their matched placebos. Daily contact with participants would enhance retention and adherence. Less promising candidates would be discarded on the basis of a series of interim reviews of safety and effectiveness so that only the best in each class and its corresponding placebo would advance into the second stage of clinical development. Turning to the current trials of oral PrEP in Thailand (tenofovir in IDUs), Botswana/South Africa (Truvada™ in heterosexuals), and in the United States (MSM, safety only), the question of drug resistance was discussed. While this will only be answered by clinical trials and post-implementation monitoring, a back-of-the-envelope calculation based on a hypothetical

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scenario suggests that the number of resistant infections will be many times less than those in the treated chronically-infected population and would be far outweighed by the number of infections prevented.

Microbicides and the Community

The crucial importance of engaging the community in the clinical trial enterprise is now widely recognized. Partnership between researchers, trial participants, and the wider community likely to be affected by, or having an influence on, the conduct of the research can both facilitate and improve the science and underpin the ethical dimensions of the entire trial process. Such engagement can reduce power disparities between researchers and the community and, more generally, between North and South. While site-based Community Advisory Boards (CABs) play an active role in the engagement process, serving as a formal link between community and researchers, these relationships can benefit from additional, often less formal, local arrangements. These were some of the points made by *Suniti Solomon (YRG Centre for AIDS Research and Education, Chennai, India)* and presented on her behalf by *Kim Dickson.* The relationship between the community (as described above) and civil society—best defined as a wide spectrum of non-governmental organizations (NGOs) and advocates active at the local, national, and/or global levels—was discussed by *Paramita Kundu (Global Campaign for Microbicides, New Delhi, India).*

Salim Abdool Karim (University of KwaZulu-Natal, Durban, South Africa) also discussed the ethical aspects of clinical trials involving vulnerable populations in developing-country settings, pointing out that such trials are more than research: they also provide care and treatment and increase local investment in and by the community. He also discussed the problems of inadequately equipped regulatory authorities and overburdened ethics committees, as well as the challenges of handling media and political reactions to bad or equivocal news.

The session concluded with a presentation by *Wu Junqing (National Population and Family Planning Commission, Shanghai, China)* about the steps being taken to improve the quality of care provided through family planning services and to expand activities to cover broader aspects of sexual and reproductive health.

The Industrialization and Regulation of Microbicides

The United States Food and Drug Administration (US FDA) has defined industrialization as the process of turning a laboratory concept into a consistent and well-characterized product that can be mass produced. *Kevin Whaley (Mapp Biopharmaceutical, Inc., San Diego, CA, USA)* drew attention to some of the complex challenges inherent in this process. These complexities tend to be underrated in the scientific community and include regulatory approval, intellectual property issues, scale-up and packaging, quality control, warehousing, and distribution. These challenges need to be addressed in parallel with the research agenda if we are to avoid unnecessarily delaying the availability of microbicides for perhaps many years.

The dangers of promoting and/or marketing products for vaginal use before they have been thoroughly scrutinized for quality, safety, and effectiveness were illustrated by several specific examples. *Henry Gabelnick* discussed the WHO/CONRAD consultation on nonoxynol-9 (N-9) that took place in 2001 in conjunction with the negative outcome of the COL-1492 trial. N-9, a surfactant, can cause epithelial disruptions, especially with high frequencies of use, and thus should not be used for STI/HIV prevention. However, it can be used for pregnancy prevention by women at low risk of infection provided that they do not engage in multiple acts of intercourse daily. Similar safety concerns may also apply to other marketed spermicides and sexual lubricants. *Judy Manning* summarized the experimental evidence that lime juice—a readily available natural product that until recently had been heavily promoted

as a potential microbicide—is unlikely to be effective against HIV if diluted to concentrations that are not harmful. The wide range of vaginal products—sexual lubricants and "pleasure enhancers," anti-infectives, and spermicides currently on the market—was illustrated by *Alan Stone* with examples from China, Europe, India, Singapore, South Africa, and the United States. Some of these products were approved by the relevant regulatory authorities, but in many cases claims regarding safety and protective activity had not been substantiated by proper evaluation. This is a matter of grave concern in the HIV/AIDS context, especially as the global penetration of Internet advertising makes this situation difficult to control.

Tim Farley referred to the challenges faced by regulatory authorities in developing countries, many of which have limited resources and rely extensively on reviews performed by better-resourced regulatory authorities elsewhere. This is not always a satisfactory solution, given that for many indications, for example HIV/AIDS prevention, the risk-benefit balance is likely to differ among countries. He outlined WHO's efforts to alleviate this difficulty and referred in particular to the series of consultations that had been convened in Asia, Europe, and Southern Africa (including the present symposium) to review microbicide science, identify minimal regulatory requirements, and explore ways of strengthening regulatory capacity. An overview of the main conclusions and recommendations from these consultations was presented by *Alan Stone*, including a summary of the non-clinical and clinical data that regulators might reasonably require in considering an application for licensure of a microbicide. Some issues remain matters for debate, including the strength of evidence required of effectiveness trials, given the contingent ethical constraints, the urgent need for preventive products, and what would constitute an acceptable trial design for evaluating microbicide combinations. *Henry Gabelnick* considered these issues in the context of the current position of the US FDA, which is willing to work proactively with industry and research groups to assist in designing studies to support approval. The regulatory scenario in India, where the Drugs Controller General is the ultimate authority, was discussed by *Badri Saxena*, while the role of South Africa's Medicines Control Council was described by *Salim Abdool Karim.*

There are some 5,000 generic drug manufacturers in China and about 176,000 drugs have been registered. Some aspects of the Chinese system of drug regulation were presented by *Wang Zongmin (FDA, Jiangsu Province, China),* who explained that provincial FDAs are subject to the rules and procedures of the State FDA. Over the past few years, a standardized application system for both generic and novel drugs has been put in place, and the arrangements for assessing the quality and bioequivalence of imported and manufactured products have been improved. Preclinical research must include studies of stability, efficacy, toxicity, and pharmacokinetics; safety is the main focus at all stages of clinical development and post-marketing. Product approval is granted initially for five years, after which re-evaluation is required. There is a special application and approval process for drugs for the treatment of AIDS and cancers. Clinical trials of new contraceptives are subject to particularly stringent requirements. Applications for the certification of vaginal products that are modifications of existing products are scrutinized by the State FDA after submission to the respective provincial authority, and all advertising material must be audited and approved.

Intellectual property (IP) issues in the international context were discussed by *Kevin Whaley*. While patents are an important driver of innovation and can protect the interests of developers, for life-saving products like microbicides it is important that creative licensing practices are deployed to ensure global access and affordability. For this to work properly, there must be effective enforcement by national governments and mechanisms for resolving disputes. *George Wang (Wilkinson & Grist, Hong Kong, Special Administrative Region of China)* spoke about the

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IP situation in China. Between 1985 and 2005, nearly 60,000 drug patent applications were filed in China, compared to 12,000 in the United States and 6,000 in Japan over that same period. Most of the patents applied for have little value, which creates a serious problem for researchers navigating the database. In 2002, China acceded to World Trade Organization (WTO) and Trade-Related Aspects of Intellectual Property Rights (TRIPS), and its IP laws were brought into conformity with international standards. Drugs, bacteria, viruses, cell lines, plasmids, protozoa, and algae are patentable, provided "absolute novelty" can be demonstrated. Methods of treatment and diagnosis, and parts of animals or plants, such as embryonic stem cells, germ cells, zygotes, and transgenic animals and plants, are not patentable. Improvements are still needed in terms of enforcement: rules of civil procedures and evidence requirements in court proceedings are not well established, there is no systematic publication of court decisions, and damages awarded are generally too low to be an effective deterrent.

Du Jenny (Regulatory Compliance Initiatives Inc./Pharmavantage, Shanghai, China) reported the results of a global survey to identify pharmaceutical companies qualified to manufacture potential microbicide products to FDA-approved Good Manufacturing Practices (GMP) standards at competitive cost. The exercise identified six such companies in China, three in India, and six in Latin America, although there may be others since many of the companies initially approached did not respond.

The correct positioning, introduction, and marketing of microbicides are critically important and culture-specific, yet failure to get these right will seriously compromise product access and acceptability. *Maggie Kilbourne-Brook (PATH, Seattle, WA, USA)* presented a detailed analysis of these issues based largely on experience with introduction of the SILCS diaphragm and the female condom. The success or failure of the first exposure of a new product to a market will affect its entire life cycle. The starting point is to define the market, which, in the case of a microbicide, could be segmented into women who might use the product for disease prevention, for pregnancy prevention, or for both. Promoting microbicides for dual protection rather than solely to prevent HIV infection is one way of reducing any stigma that might otherwise be a barrier to purchase and use. More generally, focus should be on the positive product attributes, such as lubricant, pleasure-enhancing, and personal hygiene qualities, so that ideally the product can be distributed through a wide variety of outlets, not solely through health clinics. Pricing is, of course, a critical factor.

Progress

Since the symposium, links between microbicide research teams in China have been strengthened, and efforts are under way to establish a national association for microbicide research. Collaborative links with overseas researchers have already been forged, with the international delegates at the symposium constituting a nucleus for further contacts. Chinese participation in relevant international meetings, including the *Microbicides 2010* conference to be held in Pittsburgh, PA, United States, is being encouraged. Moves are being made toward dialogue with the Chinese media about the dangers of vaginal products on the market whose safety and effectiveness have not been properly tested. Arrangements are being set up to translate into Chinese key developments reported in *News Digests* from the Alliance for Microbicide Development; the translations will be widely circulated to Chinese colleagues active in the field.

There can be no better sign of China's commitment to microbicide development than the fact that, in the weeks before the symposium, the Chinese Government announced an allocation equivalent to US$10 million for HIV prevention research, 85% of which is specifically for microbicide research and development. A further allocation will be considered in 2010 and preliminary consideration is being given to holding a second microbicide symposium around that time.

THIS QUARTER IN MICROBICIDES

1 OCT *PUBLICATION:* Shagi C, Vallely A, Kasindi S, et al. A model for community representation and participation in HIV prevention trials among women who engage in transactional sex in Africa. *AIDS Care* 20(9): 1039-49, 2008. "The community liason system (CLS) was essential to the successful conduct of the feasibility study and has now been consolidated and expanded as part of the on-going MDP301 Phase III microbicide trial in Mwanza. The participatory model presented in this paper is likely to be generalisable to other vulnerable, stigmatised, at-risk study populations in resource-limited settings."

8 OCT Dr. Gene Copello, Executive Director of The AIDS Institute, dies. Dr. Copello was also a leading member of the Caucus for Evidence-Based Prevention's Steering Committee.

13 OCT Dr. Allan Rosenfield, Dean of the Mailman School of Public Health at Columbia University, dies at age 75. "In 1985 he published, with Deborah Maine, a call to action for maternal and child health in *The Lancet*. The article, 'Maternal Mortality—A Neglected Tragedy: Where is the M in MCH?' drew attention to the many third-world women who died in pregnancy and childbirth." *The New York Times*

14 OCT CONRAD has moved! CONRAD's new address is 1911 North Fort Myer Drive, Suite 900, Arlington, VA, 22209. Phone, fax, and email addresses will all remain the same.

16 OCT IAVI publishes *AIDS Vaccine Blueprint 2008: A Challenge to the Field, A Roadmap for Progress.* "This publication is the latest in the biennial series of AIDS vaccine blueprints IAVI has produced beginning in 1998. The Blueprint aims to set the record straight about the current state of AIDS vaccine research and development and offers a series of interim targets to bring the field closer to the ultimate goal—a safe, effective and accessible AIDS vaccine." *IAVI Press Release*

20 OCT Alliance publishes *Microbicide Field Directory* online at *www.microbicide.org*. The *Field Directory* provides a comprehensive inventory of organizations involved in microbicide research, development, and advocacy. To add your organization, please email *alliance@microbicide.org*.

22 OCT *PUBLICATION:* Ramjee G, van der Straten A, Chipato T, et al. The diaphragm and lubricant gel for prevention of cervical sexually transmitted infections: Results of a randomized controlled trial. *PLoS One* 3(1): e3488, 2008. "There was no difference by study arm in the rate of acquisition of CT or GC. However, our per-protocol results suggest that consistent use of the diaphragm may reduce acquisition of GC."

31 OCT Alliance staff presentations are posted on the website. Alliance staff has given over 30 presentations at various conferences, events, and meetings since 2006. These oral and poster presentations are now available for download as PDFs at *www.microbicide.org*. Please submit comments, questions, or suggestions for future presentation content to *alliance@microbicide.org*.

1 NOV *PUBLICATION:* Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: A systematic review and meta-analysis. *Sex Transm Dis* 35(11): 946-59, 2008. "This analysis shows that infections that are associated with significant increases in leukocyte concentrations in the genital tract are also associated with significant increases in HIV-1 shedding. These infections are likely to be particularly important in promoting the sexual transmission and mother-to-child intrapartum transmission of HIV-1, and should therefore be the focus of HIV prevention strategies."

1 NOV *PUBLICATION:* Mauck CK, Ballagh SA, Creinin MD, et al. Six-day randomized safety trial of intravaginal lime juice. *J Acquir Immune Defic Syndr* 49(3): 243-50, 2008. "The brief reduction in pH after vaginal lime

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juice application is unlikely to be virucidal in the presence of semen. Lime juice is unlikely to protect against HIV and may actually be harmful."

13 NOV The International AIDS Vaccine Initiative (IAVI) celebrates the opening of its AIDS Vaccine Laboratory at the Brooklyn Army Terminal in New York.

14 NOV CAPRISA 004 Data Safety and Monitoring Board (DSMB) reviews the study data, and the outcome was: "The DSMB congratulated the study team on trial conduct and recommended that the study continue."

17 NOV *PUBLICATION:* Turner AN, De Kock AE, Meehan-Ritter A, et al. Many vaginal microbicide trial participants acknowledged they had misreported sensitive sexual behavior in face-to-face interviews. *J Clin Epidemiol* Epub ahead of print, 2008. "Researchers cannot assume that participants always tell the truth about sensitive behaviors in face-to-face interviews. ACASI was efficient and acceptable in this population."

21 NOV *PUBLICATION:* Halpern V, Ogunsola F, Obunge O, et al. Effectiveness of cellulose sulfate vaginal gel for the prevention of HIV infection: Results of a Phase III trial in Nigeria. *PLoS One* 3(11): e3784, 2008. "Cellulose sulfate gel appeared to be safe in the evaluated study population but we found insufficient evidence that it prevented male-to-female vaginal transmission of HIV, gonorrhea or chlamydial infection. The early closure of the trial compromised the ability to draw definitive conclusions about the effectiveness of cellulose sulfate against HIV."

24 NOV *PUBLICATION:* Fletcher P, Harman S, Azijn H, et al. Inhibition of HIV-1 infection by the candidate microbicide, dapivirine, a non-nucleoside reverse transcriptase inhibitor. *Antimicrob Agents Chemother* Epub ahead of print, 2008. "The prolonged protection observed following pre-treatment of genital tissue and lack of observable toxicity suggests that dapivirine has considerable promise as a potential microbicide candidate."

26 NOV *PUBLICATION:* Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* Epub ahead of print, 2008. "Universal voluntary HIV testing and immediate ART, combined with present prevention approaches, could have a major effect on severe generalised HIV/AIDS epidemics. This approach merits further mathematical modelling, research, and broad consultation."

1 DEC The world observes the 20th World AIDS Day, which brought much attention to the entire field of HIV/AIDS research, including treatment, resources, advocacy, education, and prevention.

1 DEC Michael Sidibe is named the Director of United Nations Coalition to Combat AIDS. Sidibe succeeds Peter Piot, "who has served as executive director of the group since its inception 13 years ago…Sidibe has been deputy executive director for the past two years and will assume the top post on Jan 1." *Bloomberg News*

6 DEC *PUBLICATION:* Skoler-Karpoff S, Ramjee G, Ahmed K, et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomized, double-blind, placebo-controlled trial. *Lancet* 372(9654): 1977-87, 2008. "This study did not show Carraguard's efficacy in prevention of vaginal transmission of HIV. No safety concerns were recorded."

11 DEC FDA panel recommends approval of a less expensive and quieter female condom, developed by the Female Health Company. This new version, called FC2, aims to lessen concerns of cost and noise voiced by women in the United States and internationally with the first version. FC2 will require approval by the FDA prior to moving forward with manufacturing and distribution.

MICROBICIDE CANDIDATES IN ONGOING CLINICAL TRIALS *Summary as of December 2008*

Phase	Candidate Name	MoA	Title of Study	Sponsor*	Sites by Country
3	PRO 2000/5 gel	EFI	Efficacy and safety of 0.5% PRO 2000/5 gel for the prevention of vaginally acquired HIV infection	DFID (Funder), Indevus, MRC	South Africa, Tanzania, Uganda, Zambia
2B	Tenofovir gel	RI	Safety and effectiveness of the vaginal microbicide 1% tenofovir gel to prevent HIV infection in women in South Africa (CAPRISA 004)	CAPRISA, CONRAD, FHI, Gilead, LIFElab, South African Dept. of Science and Technology, USAID	South Africa
2/2B	PRO 2000/5 gel (P) and BufferGel®	EFI, VDE	Safety and effectiveness study of the vaginal microbicides BufferGel® and 0.5% PRO 2000/5 Gel (P) for the prevention of HIV infection in women (HPTN 035)	DAIDS/NIAID, Indevus, MTN, ReProtect	Malawi, South Africa, United States, Zambia, Zimbabwe
2	Tenofovir gel	RI	Adherence and pharmacokinetics study of oral and vaginal preparations of tenofovir (MTN-001)	CONRAD, DAIDS/NIAID, Gilead, MTN	South Africa, Uganda, United States
1/2	VivaGel® (SPL7013 gel)	EFI	Assessment of local retention and duration of activity of SPL7013 following vaginal application of 3% SPL7013 Gel (VivaGel®) in healthy volunteers	NIAID, NIH, Starpharma	Australia
1	Dapivirine (TMC120) gel‡	RI	Safety and pharmacokinetics of two intravaginal dapivirine gel formulations in healthy, HIV-negative women (IPM 012)	IPM	Belgium
	Ethanol in Emollient Gel	S	Safety and acceptance of 62% ethanol in emollient gel as a topical male microbicide	NIAID	Kenya
	HEC/CS/N-9†	N/A	Assessment of markers of inflammation after vaginal product use	CONRAD/USAID	United States
	PRO 2000	EFI	Postcoital anti-viral activity of cervicovaginal secretions following intravaginal application of 0.5% PRO 2000/5 Gel (P)	AECOM, Indevus, NIH	United States
	Tenofovir gel‡	RI	Pharmacokinetic study of the vaginal microbicide agent 1% tenofovir gel (A04-095)	CONRAD, IPM/USAID	Dominican Republic, United States
	Tenofovir gel	RI	Maternal pharmacokinetics and placental perfusion of tenofovir/PMPA gel (MTN-002)	CONRAD, DAIDS/NIAID, MTN, NICHD	United States
	Tenofovir gel	RI	Effect of repeated applications of tenofovir gel on mucosal mediators of immunity and intrinsic antimicrobial activity of cervicovaginal secretions	NIAID	United States
	UC-781 gel‡	RI	Safety and persistence of 0.1% UC-781 vaginal gel in HIV-1 seronegative women	NIAID, CONRAD	United States
	UC-781 gel‡	RI	Safety and acceptability study of the UC-781 vaginal microbicide gel formulation applied rectally in HIV-1 seronegative adults	CONRAD, NIAID, UCLA	United States
	UC-781 gel‡	RI	Safety and acceptability of 0.1% and 0.25% UC-781 topical vaginal microbicide in women and acceptability in their male partners	CDC, CONRAD, Thailand Ministry of Health	Thailand
	UC-781 gel‡	RI	Male tolerance study (A06-104)	CONRAD	United States

Continued on p.22

MICROBICIDE CANDIDATES IN ONGOING CLINICAL TRIALS *Summary as of December 2008* (Continued)

Phase	Candidate Name	MoA	Title of Study	Sponsor*	Sites by Country
1	UC-781 gel‡	RI	Safety and acceptability of UC-781 topical vaginal microbicide in heterosexual women and male partners (HC 101)	CDC, CONRAD, Emory University	United States
	VivaGel® (SPL7013 gel)	EFI	Safety and acceptability of 3% w/w SPL7013 Gel (VivaGel®) applied vaginally in sexually active young women (MTN-004)**	DAIDS/NIAID, MTN, NICHD, Starpharma	Puerto Rico, United States
N/A	No Product	N/A	An observational cohort study of women following HIV-1 seroconversion in microbicide trials (MTN-015)	DAIDS/NIAID, MTN	Malawi, South Africa, Uganda, Zambia, Zimbabwe
	Placebo ring±	Placebo	Safety and acceptability of a placebo vaginal ring microbicide delivery method for the prevention of HIV infection in women (IPM 011)	IPM	South Africa, Tanzania (ongoing sites); Kenya (follow-up)

Definition of acronyms used in this table: Mechanism of Action (MoA), Entry/Fusion Inhibitor (EFI), Replication Inhibitor (RI), Vaginal Defense Enhancer (VDE), and Surfactant (S)

**The Alliance uses the term "sponsor" as defined by the International Conference on Harmonisation (Guideline for Good Clinical Practice, 1996) as follows: "An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."*
†HEC, CS, and N-9 are not in development as microbicides. Rather, this trial's objective is to characterize inflammation and genital epithelial changes in healthy, sexually abstinent women before, during, and after 13½ days of twice-daily applications of one of three products: a hydroxyethylcellulose (HEC)-based "universal" placebo, 6% cellulose sulfate, or 4% nonoxynol-9 (Conceptrol®) gel; to determine the degree of correlation between different methods of clinical assessment; and to determine the degree of correlation between the results of this clinical study and the results of the preclinical assessment of the same compounds. This trial is currently in data analysis.
‡ These trials have completed clinical studies, but data analysis is ongoing.
***ATN 062, "Tell Juliana," is an observational study taking place in parallel to MTN-004. Please visit the MRDD for further information on this ancillary study.*
± This device is intended for use with a microbicide.

MICROBICIDE CANDIDATES AND ANCILLARY DEVICES IN PLANNED AND FUNDED CLINICAL TRIALS *Summary as of December 2008*

Phase	Candidate Name	MoA	Title of Study	Sponsor*	Sites by Country
3	BufferGel®	VDE	Trial of the diaphragm with a candidate microbicide to prevent sexually transmitted infections (MIARADIA)	CDC, CONRAD, NIAID/NIH, UNC, UNC-MD, USAID	Madagascar
3	Dapivirine (TMC120)	RI	Dapivirine efficacy study (IPM 009)	IPM	Various
2/3	Invisible Condom®	EFI	Effectiveness of Invisible Condom® in high-risk women		*Sites in Africa TBD*
2/2B	Tenofovir gel	RI	Safety and effectiveness of tenofovir 1% gel (PMPA) with two oral HIV prevention approaches - tenofovir and Truvada™, a tenofovir-FTC drug combination (MTN-003 – VOICE)‡	CONRAD, DAIDS/NIAID, Gilead, MTN, NICHD, NIMH	Kenya, Malawi, Rwanda, South Africa, Tanzania, TBD
1/2	Dapivirine (TMC120)	RI	Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women (IPM 014A)	IPM	Kenya, Malawi, Rwanda, South Africa, Tanzania, TBD
	Dapivirine (TMC120)	RI	Safety and acceptability of dapivirine gel, conducted using daily monitored adherence in healthy HIV-negative women (IPM 014B)	IPM	Kenya, Malawi, Rwanda, South Africa, Tanzania

Continued on p.23

MICROBICIDE CANDIDATES AND ANCILLARY DEVICES IN PLANNED AND FUNDED CLINICAL TRIALS *Summary as of December 2008* *(Continued)*

Phase	Candidate Name	MoA	Title of Study	Sponsor*	Sites by Country
1/2	Dapivirine (TMC120)	RI	Safety of an intravaginal matrix ring with dapivirine for the prevention of HIV infection in healthy HIV-negative women (IPM 015)	IPM	Kenya, Malawi, Rwanda, South Africa, Tanzania, TBD
	Dapivirine (TMC120)	RI	Dapivirine gel expanded safety study (IPM 020)	IPM	United States
	Dapivirine (TMC120)	RI	Dapivirine intravaginal ring expanded safety study (IPM 021)	IPM	Germany, Netherlands, United Kingdom
1	CAP vaginal soft tablet	C	Safety and acceptability of CAP vaginal microbicide soft tablet	New York Blood Center, NIAID	United Kingdom
	Dapivirine (TMC120)	RI	Dapivirine gel male tolerance study (IPM 010)	IPM	TBD
	Dapivirine (TMC120)	RI	PK study in healthy HIV-negative women to assess delivery of dapivirine from intravaginal rings (IPM 013)	IPM	Belgium
	Dapivirine (TMC120)	RI	Study to evaluate effect of dapivirine gel on vaginal flora (IPM 023)	IPM	Belgium
	Duet®	C	Duet® acceptability and safety study	IPM, ReProtect, RTI International	Zimbabwe
	PC-815	C	Randomized, double blind, crossover safety study of two microbicide formulations: PC-815 and Carraguard®	Population Council	Dominican Republic, South Africa
	Tenofovir/PMPA gel	RI	Device for Vaginal Drug Delivery (DVD2) with tenofovir gel vs. plain tenofovir gel	FHI	
N/A	Placebo ring	Placebo	Expanded safety and acceptability study of a non-medicated intravaginal ring (MTN-005)	DAIDS/NIAID, IPM, MTN	India, United States
	No product	N/A	Seroconverter protocol (IPM 007)	IPM	
	Placebo	Placebo	Pilot study to evaluate the accuracy of the Smart applicator for microbicide clinical trials (IPM 022)	IPM	South Africa, United States

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Definition of acronyms used in this table: Mechanism of Action (MoA), Entry/Fusion Inhibitor (EFI), Replication Inhibitor (RI), Vaginal Defense Enhancer (VDE), and Combination (C)

**The Alliance uses the term "sponsor" as defined by the International Conference on Harmonisation (Guideline for Good Clinical Practice, 1996) as follows: "An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial."*
‡This study includes an observational cohort study (MTN-003B), entitled Bone Mineral Density Substudy, which will explore the effects of oral study products on bone mineral density.

THE MICROBICIDE QUARTERLY

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