Pregnancy Management and Contraceptive Care Issues in Biomedical HIV Prevention Trials

Bridget Hanes, MPH
Department of Prevention and Community Health
School of Public Health and Health Services
George Washington University

Amita N. Vyas, PhD
Assistant Professor
Department of Prevention and Community Health
School of Public Health and Health Services
George Washington University

Monica Ruiz PhD
Assistant Research Professor
Prevention Research Director, Forum for Collaborative HIV Research
School of Public Health and Health Services
George Washington University

THE GEORGE WASHINGTON UNIVERSITY
SCHOOL OF PUBLIC HEALTH AND HEALTH SERVICES

This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID). The contents are the responsibility of the Forum for Collaborative HIV Research and do not necessarily reflect the views of USAID or the United States Government.

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Executive Summary

Background

The HIV pandemic is increasingly becoming a burden on women, especially women of reproductive age. Currently available HIV prevention techniques often are not feasible for many women. A toolbox of diverse prevention options is crucial to help women protect themselves from HIV infection. Working toward this goal, clinical research is underway on woman-initiated methods, such as microbicides and pre-exposure prophylaxis (PrEP), for HIV prevention . Microbicide and PrEP trials enroll sexually active women of reproductive age typically in areas with high fertility rates. As higher than anticipated rates of pregnancy have occurred in some microbicide and PrEP trials, growing attention has been placed on study-related pregnancy management and contraceptive care issues. According to UNAIDS/WHO, biomedical HIV prevention trials should provide to trial participants "appropriate reproductive and sexual health counseling and ancillary services, including family planning" and "care and treatment practices should include reproductive health care for pregnancy and childbirth".

Aims

This project explores: (1) the study-related practices concerning pregnancy management and contraceptive care provided to trial participants in ongoing and planned phase II and III clinical microbicide and pre-exposure prophylaxis (PrEP) trials; and (2) current perceptions of practices or services related to pregnancy management and contraceptive care in ongoing and planned phase II and III clinical microbicide and PrEP trials.

Methods

Key informant phone interviews were conducted with professionals working in a leadership capacity, such as Protocol Chair or Study Director, on microbicide or PrEP trials. The trials included in key informant interviews were chosen based on the criteria that they: 1) were ongoing or planned as of August 2008; and 2) were in either phase II or III; and 3) involved heterosexual female study participants of reproductive age. Twenty minute phone interviews were conducted with nine key informants representing seven microbicide and PrEP trials.

An anonymous online survey was created on Survey Monkey and sent out via multiple list serves composed of professionals working in the field of HIV, reaching over 800 recipients. The total project sample for the survey was 106. The survey consisted of 20 questions in total, with 5 multiple choice background questions, and 15 Likert-scale items pertaining to pregnancy or contraceptive issues during trials, and 5 open-ended questions also relating to pregnancy and contraceptive issues.

Results

Key Informant Interviews

Overall, the microbicide and PrEP trials represented in the key informant interviews share many practices and services related to pregnancy management and contraceptive care in trials, although many variations exist across trials regarding the approaches the different trials take to implement these practices and services.

Summary of PrEP and microbicide trials meeting criteria related to pregnancy management and contraceptive care

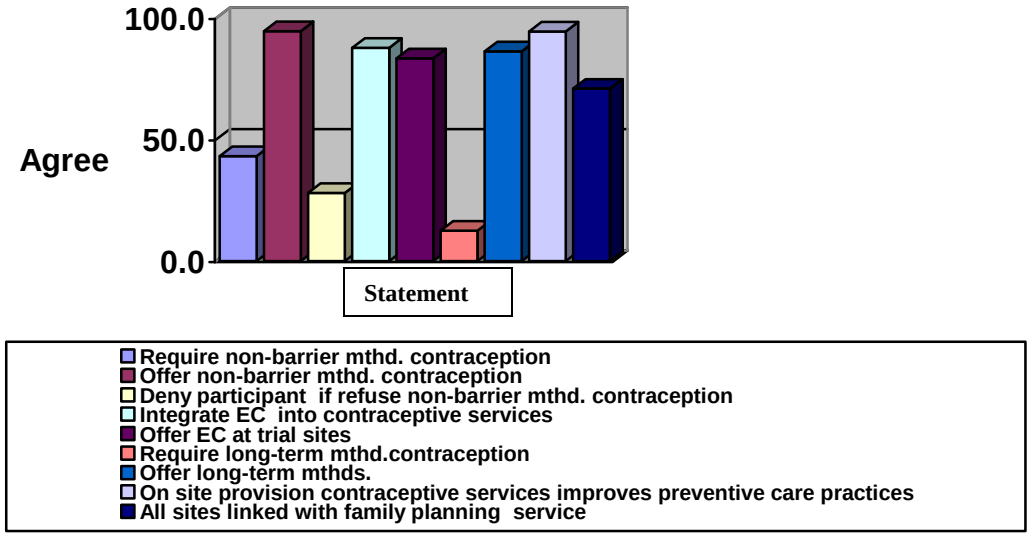
Criteria	# of Prep Trials (n=5)	# of Microbicide Trials (n=2)
Exclude pregnant women	5	2
Exclude breastfeeding women	5	0
Exclude women w/pregnancy intentions	5	2
Require effective contraception	4	1
On site provision of contraception	5	2
Refer out for contraception not available on site	5	2
Record use of contraceptive methods by participants	4	2
Emergency contraception available on site	1	1
Provision of contraceptive counseling on site	5	2
Pregnancy testing at least once a month	5	2
Discontinue product use with positive pregnancy test	5	2
Continue most other study services during pregnancy	4	2
Permit participant to return to product use with negative pregnancy test	0	2
Permit participant to return to product use with negative pregnancy test and no longer breastfeeding	3	0
Refer participants testing positive for pregnancy to antenatal care	5	2
Provide participants testing positive for pregnancy with pregnancy options counseling	0	1
Track pregnancy outcomes	5	2
Track all infants past birth outcomes	1	0
Track infants past birth outcome if abnormalities at birth	1	0

Survey

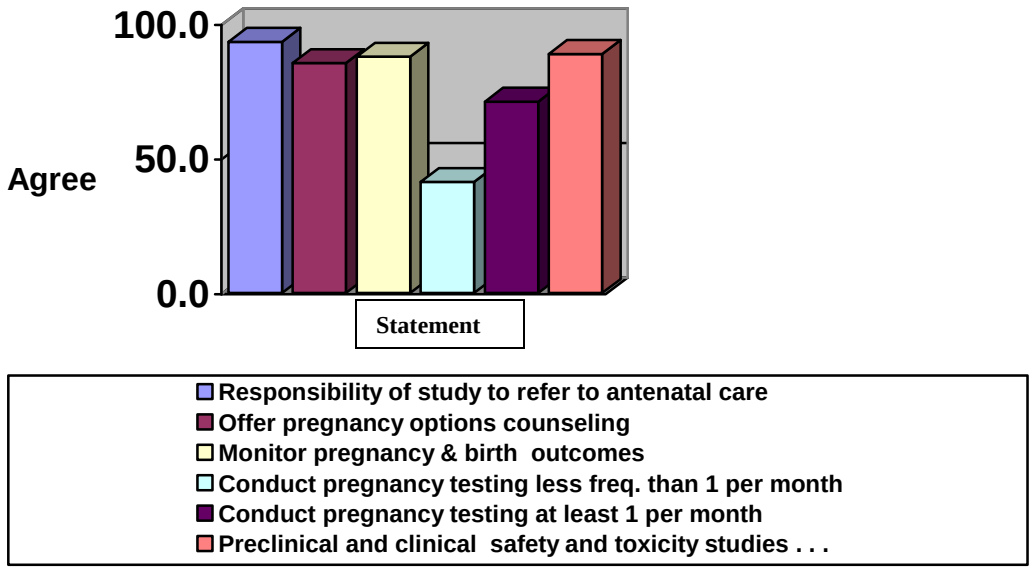
The total project sample (n=106) for the survey was composed primarily of professionals working in social and behavioral research and advocacy; working in a NGO or university settings; holding MPH or PhD degrees; and performing work primarily in North America and sub-Saharan Africa. Over half of the sample was involved in work in HIV prevention trials.

The results for the survey demonstrate that professionals working in the field of HIV are in general agreement about issues relating to pregnancy management and contraceptive care. However, when the sample is broken down into professionals involved in work on HIV prevention clinical trials and professionals not involved in work on HIV prevention clinical trials, a few differences in perception emerge for specific statements relating to pregnancy management and contraceptive care. The largest difference in perception was found for the statement that "participants should be denied participation in a trial if they refuse to use a non-barrier contraceptive method".

Percent of total sample (n=106) that agrees/strongly agrees with each statement related to contraceptive issues in clinical HIV prevention trials



Percent of total sample (n=106) that agrees/strongly agrees with each statement related to pregnancy issues in clinical HIV prevention trials



Recommendations

- Continue to increase priority for the integration of reproductive and sexual health care, including pregnancy management and contraceptive care, in clinical HIV prevention trials.
- Proactive and thoughtful efforts needed to balance the safety and well-being of participants and their fertility choices with the needs of clinical trials.
- Implement different approaches for measuring pregnancy wantedness and intentions prior to study enrollment
- Expand opportunities for dialogue among professionals working in HIV prevention in order to share knowledge and experiences that could enhance pregnancy management and contraceptive care practices in ongoing and planned clinical HIV prevention trials.
- Continue to work toward diversification of effective contraceptive methods available to trial participants through direct on-site provision in order to provide participants with more choices.

- Further research on the quality of contraceptive provision and counseling provided to participants in HIV prevention trials to determine which approaches are working well, and the sharing of these approaches across clinical HIV prevention trials.
- Invest in the strengthening of contraceptive counseling and pregnancy management training for clinical staff in order to enhance the quality of contraceptive care and counseling provided to study participants.
- Increase discussion regarding pregnancy options counseling, even at site locations where abortion is illegal, so study staff is prepared to deal with this often sensitive issue as appropriately as possible in order to protect the well-being of study participants and the accuracy of data collection.
- Further research on the viability of integrating emergency contraception into contraceptive care practices at trial sites.

I. Background

A. The HIV Epidemic and Women

Globally, 33 million people are infected with HIV, with 2.7 million new infections and 2.0 million deaths occurring in 2007.[1] The percentage of women living with HIV globally has remained stable around 50% for the past decade, although several countries have seen an increase in HIV infections among women.[2] In sub-Sahara Africa, women account for nearly 60% of all HIV infections.[2] Young women are particularly affected with almost one half of all new infections worldwide occurring among individuals between the ages of 15-24, and women accounting for 62% of young people living with HIV/AIDS.[3] Even in low prevalence areas such as China, the male-to-female sex ratio has narrowed from 9:1 in the 1990s to 3:1 in 2003.[4]

The HIV pandemic is increasingly becoming a burden on women, especially women of reproductive age. The increasing proportion of women living with HIV around the world has often been called the "feminization" of the HIV epidemic. Gender inequity is often at the core of this phenomenon. In sub-Saharan Africa and other regions around the world, women and girls often live in a context of low social status, sexual violence and coercion, and unequal access to legal protection, education, economic opportunities as well as health services and information.[3]

Currently available HIV prevention techniques often are not feasible, especially for many women. In many countries, married and monogamous women may be at one of the highest risks for infection.[5] Women may not have a say in their sexual practices and their male partners may not be open to use of condoms. Often couples may wish to have children, and therefore refrain from condom use. Research has also shown that women are biologically more susceptible to HIV transmission. Male-to-female transmission is more than twice as likely to occur as female-to-male transmission because of biological difference.[6] This biological vulnerability combined

with social, economic, and cultural factors are driving the HIV/AIDS epidemic in the female population.[3]

Although remarkable progress has been made in knowledge of HIV prevention and treatment over the past several decades, the HIV virus continues to spread at alarming rates. The number of new HIV infections continues to exceed the increase each year in the number of people on antiretroviral drugs by 2.5 to 1.[2] Clearly, extensive efforts are needed in preventing new HIV infections and a toolbox of diverse prevention options is crucial to help women protect themselves from HIV infection.

B. Woman-initiated methods of HIV prevention: Vaginal Microbicides and PrEP

One woman-initiated method of HIV prevention is vaginal microbicides. Microbicides are products that can be applied inside the vagina and have the ability, if proven effective, to prevent sexually transmitted infections (STIs) including HIV. Microbicides could be produced in many forms, including gels, creams, suppositories, films, or as a sponge or ring that releases the active ingredient over time. Some microbicide candidates with contraceptive potential are being tested, while others are non-contraceptive. According to the Global Campaign for Microbicides, microbicides would be "the most important innovation in reproductive health since the Pill."[7] Mathematical modeling predicts that even a partially effective microbicide could prevent millions of new infections.[8]

Although no safe and effective microbicide is currently available to the public, researchers are pursuing approximately 50 product leads with 11 products that have been proven safe and effective in animals and are underway in clinical trials in people.[7] Clinical trials are separated into three phases:

- Phase I: Small studies, usually enrolling 20 to 40 healthy volunteers, to test for safety, side effects, and proper dosage of a candidate product for a limited period of time (1-2 weeks).
- Phase II: Larger studies, usually enrolling 200 to 400 volunteers. They look for further safety issues and side effects of the candidate product for a longer period of time (6-18 months). Phase II studies also offer some information about acceptability of the product. Phase IIb studies involve 200-800 volunteers, usually for 6-12 months, and are specifically designed to study safety and efficacy (to see if the candidate drug works as intended).
- Phase III: Also known as an efficacy/effectiveness trials, these are large studies enrolling thousands (3,000-10,000) of volunteers. This phase continues to test for safety and determine efficacy (to see if the candidate drug works as intended).[9]

While most products remain in the preclinical or phase I safety trials, three products – PRO 2000/5 gel, Tenofovir/PMPA gel, and BufferGel – are in phase II or III clinical trials involving heterosexual women to determine if the products prevent HIV infection through vaginal intercourse.[10] Three other products – Dapivirine (TMC120), ADIDFORM/Amphora, and Invisible Condom – are in the planning stages for phase II or III clinical trials.[11] Since 2005, three other candidate microbicides – Cellulose Sulfate, SAVVY, and Carraguard – have been discontinued from trials for different reasons. Early data from the Cellulose Sulfate trials were suggested that the product may increase risk of HIV infection. The SAVVY trials were terminated due to low incidence of HIV in the study population and early data showing that it

was unlikely that the product had a protective effect against HIV infection. The Carraguard trial results showed that the product was not effective in reducing the risk of acquiring HIV.[12]

Researchers have been testing candidate microbicide products with different mechanisms of action to prevent HIV infection. First-generation microbicides, including BufferGel and Pro-2000/5, are called either non-specific microbicides or broad-spectrum microbicides meaning they target a range of different viral and bacterial pathogens, including HIV. They work by changing the chemistry of the vagina in different ways to make infection less likely. Non-specific microbicides can work through three different mechanisms of action: (1) blocking agents that prevent the virus or pathogen from entering cells; (2) vaginal defense enhancers that boost the body's natural defenses; and (3) membrane disrupting agents that inactivate the virus or pathogen.[13] These products are made into a gel and applied vaginally. They are considered coitally dependent because they are applied just before sex.

Next- or second-generation microbicides, including Tenofovir and Dapivirine, contain an antiretroviral (ARV) drug that is specific to HIV. These ARV-based microbicides work through two primary mechanisms of action: (1) entry inhibitors that either block specific proteins on the virus or block specific receptors on target cells; or (2) replication inhibitors that either inhibit the reverse transcriptase enzyme from initiating replication (NNRTIs) or inhibit the replication process once it has started (NRTIs).[13] These microbicides are being tested for coitally-dependent and independent use. One of the advantages of coitally independent microbicides is that they could be used once a day, and it is believed that compliance would be higher than with coitally dependent use.[14]

Another prevention approach, which also addresses the need for woman-initiated methods, is pre-exposure prophylaxis (PrEP). PrEP refers to an experimental HIV-prevention

strategy that would use ARV drugs to protect HIV-negative people from infection. The concept behind PrEP is for HIV-negative individuals to take ARVs, or a combination of ARVs, daily in the hopes that this would protect them against HIV infection. PrEP is not yet proven to work but, along with microbicides and HIV vaccines, is being tested in clinical trials today as another method for HIV prevention.

Currently, there are six ongoing or planned phase II or III PrEP trials with female heterosexual participants – MTN-001, MTN-003/VOICE, FEM-PrEP (Truvada), Partners PrEP, the Bangkok Tenofovir Study, TDF2 trials. *(See Chart A for more information on trials).* Two of these trials, the MTN-001 and MTN-003, are testing vaginal microbicide candidates concurrently with PrEP candidates. One mathematical model suggests that, under an optimistic scenario, a PrEP strategy could reduce the cumulative rate of new HIV infections by 74% after 10 years.[15]

C. Challenges Facing Microbicide and PrEP HIV Prevention Trials

High Pregnancy Rates

Several clinical trials have had higher than anticipated rates of pregnancy. Rates for completed, terminated, or ongoing microbicide or PrEP trials range from a low of 16 to a high of 64 pregnancies per 100 women-years.[16] ,[17],[18] These varied rates could result from many possible factors, including: (1) detection of chemical pregnancies due to increased frequency of pregnancy testing; (2) lack of stringent criteria for contraceptive use and consequently use of unreliable contraceptive methods; (3) inadequate counseling of participants and lack of contraceptive services at trial site; and (4) fact that high rates of pregnancy are unavoidable given most participants are in peak reproductive age.[19]

To date, phase II and III microbicide and PrEP trials have excluded pregnant women and required women who become pregnant during the trial to discontinue product use due to safety

concerns for use by pregnant women. Discontinuing product use in women who become pregnant during the trial has implications for trial design, conduct, and generalizability of trial results.[20] Unanticipated high rates of pregnancy can complicate data analysis and impact the statistical power of studies to determine if a product actually works to prevent HIV infection.[21] Additionally, discontinuing product use in women who become pregnant makes interpretation of trial results difficult as any product found to have proven efficacy will be used by women who become pregnant.[20]

Safety of investigational products during pregnancy

Historically, regulatory agencies and sponsors have excluded women of childbearing potential and pregnant women from trials of new products without known benefits to humans. Such protectionist regulations excluding women of childbearing potential from drug testing were put in place by the FDA in 1977 in response to the harmful effects that certain drugs, such as thalidomide and DES, caused to babies born to women who were prescribed these drugs, without the supporting scientific data to do so, during pregnancy.[22] However, in the 1990s the FDA began to revise the guidelines allowing for women of childbearing potential to join trials based on a standard of informed consent.[20]

The assumptions that pregnant women should be excluded from trials have also been challenged by different authorities. In 2001, the Department of Health and Human Services (DHHS) issued guidelines abandoning the universal exclusion of pregnant women, with the caveats that preclinical studies must have been completed on the study product and the product must have a prospect of benefit or the perceived fetal risk is minimal and there is no other way to generate important biological knowledge.[20] A recent Institute of Medicine (IOM) report, *Methodological Challenges in Biomedical HIV Prevention Trials*, included in its key

recommendations: (1) the need for evaluating the potential effects products may have on pregnant women and their fetuses and (2) that regulatory agencies and investigators consider allowing pregnant women to continue participation in clinical research under some circumstances.[20] The UNAIDS/WHO guidance document, *Ethical considerations in biomedical HIV prevention trials*, agrees that women who "may become pregnant, be pregnant or be breastfeeding . . . should be eligible for enrollment in biomedical HIV prevention trials."[23] The International Conference on Harmonization (ICH) has issued guidelines that all reproductive toxicology studies be completed before enrolling women with childbearing potential who are not on effective birth control, whose pregnancy status is unknown, or women who are pregnant.[20] The IOM recommends that reproductive toxicity studies be completed before the product enters phase II testing, and no later than phase III testing.[20] The IOM has also recommended that evaluations should be done on a product-by-product basis to evaluate whether there are circumstances in which women who become pregnant can continue to receive the study product, based on what is known about its benefits and risks.[20]

Although under some circumstances pregnant women may be allowed to participate in clinical trials, at this point in time microbicide and PrEP trials exclude pregnant women from enrollment and remove women who become pregnant from study product. Data is lacking for use of these products during pregnancy and testing of the candidate products in pregnant women has not been completed

Nonetheless, excluding pregnant women from trials or removing women who become pregnant during trial from product raises ethical concerns. In a real-world setting, any product that proves successful and is available to the public will most likely be used by women after they become pregnant. According to some researchers, the study of drugs during pregnancy is one of

the most neglected areas of biomedical research.[24] This gap in research is concerning to many researchers because the same population of women at risk for HIV is also the population of women most likely to become pregnant.[24] In addition, research has found that pregnant women may be at even greater risk for HIV infection through sexual intercourse than women who are breastfeeding, or neither pregnant nor breastfeeding.[25] Limiting trials to non-pregnant women will not provide data on efficacy and safety of microbicide use in pregnant women. In addition, excluding pregnant women from trials means that an entire class of people that could benefit from a product is at an unfair disadvantage.[26]

In response to the lack of safety data on microbicide use in pregnant women, researchers from the Microbicide Trials Network (MTN) and the University of Pittsburgh have developed the first clinical trial to test a candidate vaginal microbicide in pregnant women. The phase I study, known as MTN-002, will test one-dose of the ARV-based candidate microbicide called tenofovir gel in 16 healthy HIV-negative women approximately two hours prior to giving birth by scheduled cesarean delivery. Researchers will seek to understand the pharmacokinetics and placental transfer of tenofovir gel in pregnant women; in other words, they will be looking at the extent that pregnancy affects how the body absorbs and distributes the drug and whether the drug can be transferred to the fetus. This trial is the first step toward determining if use of a vaginal microbicide is safe for pregnant women and their fetuses. The study is expected to be completed in 2009.[27] If data from the MTN-002 trial demonstrate safety for use during pregnancy, efficacy trials with tenofovir gel could potentially allow women who become pregnant to remain in the study and continue to use the product.

Pregnancy prevention in clinical HIV prevention trials

Preventing pregnancy in clinical trials is a challenge for many reasons, one of which is that the populations participating in clinical HIV prevention trials typically have a high background pregnancy rate.[20] Pregnancy prevention practices have not always been a central focus of clinical HIV prevention trials. However, even in trials in which reported use of condoms and contraception was high, extremely high rates of pregnancy have occurred.[17] After high rates of pregnancy began to take place in trials, the issue of pregnancy in trials began to gain increasing attention among trial researchers.[28] Absent safety data for investigational product use by pregnant women, pregnancy is a real issue of concern in clinical HIV prevention trials. Research has shown that condom use alone is not sufficient as the only method of contraception for women with high frequency of sexual encounters.[17]

Some researchers have suggested that trials should mandate use of an effective non-barrier method (which typically includes birth control pills, injectables, implants, intrauterine devices (IUDs), and sterilization of participant or her partner) for all female participants with reproductive potential.[29] Others believe trials should provide effective methods, but not require effective contraceptive use, in order to maintain participants' autonomy in regards to reproductive health decisions.[18] Planned and ongoing trials have begun to adopt both of these approaches as well as others to prevent pregnancies from occurring during clinical HIV prevention trials.

Tracking Pregnancy Outcomes

Additional challenges arise during trials, such as tracking and monitoring pregnancy outcomes. Researchers have sometimes ceased to follow women who become pregnant for pregnancy and HIV outcomes, thereby failing to track product effects on pregnant women and

their fetuses.[30] The UNAIDS/WHO guidance document states that researchers should "maintain pregnancy registries to collect data on outcomes of pregnancies that inadvertently occur during the trial, [and] follow-up babies born to women participants."[23] In response to concerns about lack of safety data of candidate products during pregnancy, the MTN has started an HIV Prevention Agent Pregnancy Exposure Registry called MTN-016. The registry's primary and secondary goals are to: (1) evaluate the safety and teratogenic risk of investigational products and to monitor the prevalence of structural abnormalities in fetuses and infants; and (2) provide evidence-based assurance of lack of teratogenic risk when a given test product is used during pregnancy. This trial will enroll women who were exposed to a microbicide or PrEP agent when they became pregnant while participating in an HIV prevention trial.[31]

D. Project Rationale

Over the past decade, advocates in the international community have been pushing to improve the integration and strengthening of linkages between HIV prevention services and sexual and reproductive health services.[32] Although clinical HIV prevention trials have the primary goal of testing new drugs and products to see if they will protect against HIV infection, these trials should not neglect the reproductive and sexual health needs of the trial participants. UNAIDS/WHO stated in a guidance document for biomedical HIV prevention trials that "appropriate reproductive and sexual health counseling and ancillary services, including family planning, should be provided to trial participants"[23] and care and treatment practices should include reproductive health care for pregnancy and childbirth.[23] Nonetheless, numerous completed or terminated biomedical HIV prevention trials have lacked focus on fertility-related issues.

Trial sponsors and planners for ongoing and planned trials have been focusing ever-increasing attention on issues of pregnancy management and contraceptive care. This project will

add to the current discussions around pregnancy management and contraceptive care in clinical HIV prevention trials by: (1) exploring the related care practices and services of ongoing and planned microbicide and PrEP trials; and (2) exploring perceptions held by professionals in the HIV field regarding pregnancy management and contraceptive care in clinical HIV prevention trials.

II. Aims

1. To examine study-related practices for pregnancy management and contraceptive care provided to trial participants in ongoing and planned phase II and III clinical microbicide and PrEP trials and the related challenges. For example, to explore practices and services related to:
    - inclusion and exclusion criteria related to pregnancy and contraceptive use;
    - provision of contraception, contraceptive counseling, and requirements for contraceptive use;
    - pregnancy testing;
    - product use;
    - pregnancy-related care; and
    - tracking and monitoring of pregnancies occurring during trials.
2. To asses current perceptions of practices or services related to pregnancy management and contraceptive care in ongoing and planned phase II and III clinical microbicide and PrEP trials and the related challenges. For example, to explore practices and services related to:
    - inclusion and exclusion criteria related to pregnancy and contraceptive use;
    - provision of contraception, contraceptive counseling, and requirements for contraceptive use;
    - pregnancy testing;
    - product use;

- pregnancy-related care; and
- tracking and monitoring of pregnancies occurring during trials;

III. Methods

A. Data Collection

1. Key Informant Interviews

To meet the first aim, key informant interviews were conducted with professionals working on microbicide and/or PrEP trials. The sample for the key informant interviews was initially identified through Internet research and contacted via email correspondence. The professionals in the sample worked on trials in the capacity of Principal Investigator, Individual on Record, or Study Director or in other clinical leadership or oversight capacities. The sample of key informants was selected based on the criteria that they were working on microbicide or PrEP trials that: 1) were ongoing or planned as of August 2008; and 2) were in either phase II or III[1]; and 3) involved heterosexual female study participants of reproductive age. Twelve trials met these criteria. Contact information for the key informants was collected through Internet research and successfully located for 10 of the 12 trials. A total of 19 key informants, with at least one individual from each of the 10 trials, was contacted via email with information about the purpose of the key informant interviews and asked if they would be willing to participate. Interviews were scheduled via email correspondence.

[1] Phase I trials were not included in this research because they are usually short in duration and have high adherence to condom use (Joshi, S. and Mehendale, S. Clinical safety issues in developing and testing of vaginal microbicides. *Indian J Med Res* 2006*;* 123:5), thereby removing concerns relating to pregnancy management or care.

The final study sample of nine key informants representing seven different microbicide and PrEP trials each participated in a 20 minute phone interview. *(See Chart A for more details on the trials).* The interview consisted of questions focusing on two broad domains: pregnancy issues and contraceptive issues. In addition, a focus was placed on challenges that exist or are anticipated to exist during the trials within each of these domains.

Protocol documents for the seven trials represented in the key informant interviews were located through Internet research when possible. When not available online, protocols were requested from the key informants. We were able to obtain protocol documents for the seven trials included in the key informant interviews.

2. Quantitative Survey

To meet the second aim, an anonymous online survey was created on Survey Monkey. The survey was sent via email to multiple list serves composed of professionals working in the field of HIV, reaching over 800 recipients.[2] The sample for the survey was composed of professionals working primarily in the field of HIV as community advocates, researchers, scientists, policy makers, policy analysts, sponsors of research, media, and service providers working in private, governmental, and non-governmental organizations. The sample worked in the areas of HIV care, prevention, treatment, advocacy, research, and information-management; gender equality; sexual and reproductive health and rights; poverty and economic development; and human rights. The total number of respondents for the survey was 106 (n=106), with 60.4% of respondents completing all survey items.

[2] It is unclear to what extent each individual received the survey more than once, but it is assumed that individuals in this field are often members of multiple list serves and most likely received the email multiple times.

The survey consisted of 25 items, composed of five multiple choice questions, 15 Likert-scale statements, and five open-ended items. The five multiple choice items focused on the participants' background information. The remaining 20 items were focused on the two key domains of pregnancy and contraceptive care issues. Participants were not required to answer any of the questions in order to progress through the survey. Each multiple choice and Likert-scale statement allowed for participants to provide a comment.

B. Analysis

1. Key Informant Interviews

Each key informant interview was transcribed. Each transcript was reviewed for information pertaining to the two primary domains of pregnancy and contraceptive care issues. Each domain was broken down into sub-themes. The four sub-themes under the pregnancy issues domain include: (1) enrollment criteria concerning pregnancy; (2) practices for when pregnancy occurs; (3) pregnancy testing; and (4) pregnancy tracking and monitoring. Under contraceptive issues, the three sub-themes include: (1) enrollment criteria concerning contraception; (2) provision of contraception; and (3) contraceptive counseling. Protocols and other study-related documents were also reviewed to supplement information provided by key informants and fill in any gaps where possible. A chart was created listing many of the practices and services falling under the two primary domains in order to facilitate comparison of practices and services across the different trials *(See Chart B)* and a second chart was created to show the number of trials that provide the different practices and services *(See Chart C)*.

2. Quantitative Survey

Survey responses were entered into Excel. For ease of examining trends, the percentages for the 15 Likert items were combined for 'strongly disagree' with 'disagree' and 'strongly agree' with 'agree'. Descriptive analysis was used to present the survey results.

IV. Results

A. Key Informant Interviews

(See Chart B for Summary of Key Informant Results Chart)

1. Pregnancy Issues: Sub-themes

Enrollment criteria relating to pregnancy:

- All seven of the ongoing or planned microbicide and PrEP trials included in key informant interviews in this project exclude pregnant women from participation in trials. The reason given by all key informants who discussed this exclusion was for safety reasons for the pregnant woman and fetus.
- Seven trials exclude women who indicate that they plan to get pregnant during study duration. One key informant indicated that although there is an exclusion criterion for pregnancy intention in the trial, she is not convinced from experience in clinical trials that "intentions really map out behavior anyway" (Partners PrEP).
- Five trials exclude women who are breastfeeding from enrollment. All five of these trials are PrEP trials that include the oral antiretrovirals tenofovir (TDF) and/or a combination of tenofovir and emtricitabine (TDF + FTC, also known as Truvada). Two trials, CAPRISA 004 and HPTN 035, do not exclude breastfeeding women from enrollment. The candidate product being tested in the CAPRISA 004 trial is tenofovir gel. According to a key informant for this trial, the reason for allowing breastfeeding women in the trial is that "the safety data we have from previously conducted trials shows that the product is largely remaining in the genital track without systemic absorption . . . so we didn't feel that this would be getting into the breast milk" (CAPRISA 004). However, a key informant from the MTN 003/VOICE trial spoke about the exclusion of breastfeeding women, including those randomized to the vaginal gel or placebo gel, and said that the reason for exclusion is that although "the gel is minimally systemically absorbed, our data show you can detect it in the blood" and indicated that the trial does not want to worry about that possibility (MTN 003/VOICE). Another trial, the MTN 001, explains in the protocol documents that "it is unknown if there are any effects of tenofovir on breast milk" and "it is not known if tenofovir tablets or gel will pass through breast milk and cause harm to your infant." (MTN001 protocol, pg 130). The HPTN 035 trial is testing two candidate products, BufferGel and PRO 2000/5 Gel, and according to the key informant the two products they are studying "are not known to be systemically absorbed". (HPTN 035)

Practices for when pregnancy occurs:

- All seven trials immediately take participant off of study product with a positive pregnancy test.
- Six trials keep women who become pregnant in the study follow-up and continue to provide other trial-related services and testing appropriate during pregnancy to these participants. The key informant for Partners PrEP explained that participants who test positive for pregnancy continue all other study services and all other protocol required testing. (Partners PrEP) The key informant for the MTN 001 trial explained that participants remain in study follow up until their scheduled end date. The key informant for CAPRISA 004 explained that participants remain on other study services, but do not collect blood or vaginal specimens tests during pregnancy because participant is not on product (CAPRISA 004). The Fem Prep key informant explained that participants are not discontinued from study follow up. (FEM PrEP) The HPTN 035 consent forms explain that the study will "change the study procedures as needed to protect your health while you are pregnant. For example, we will not examine or collect fluids from your vagina after 24 weeks of pregnancy." (HPTN 035 protocol, pg 132) One trial, the Bangkok Tenofovir Study, does withdraw participants who become pregnant from the study. The key informant explained that they have so few women (approximately 20%) in the trial and that there are "so few pregnancies that removing women who become pregnant from the trial is not going to compromise the trial." In addition, the key informant explained that being removed from the study does not limit these participants from accessing the clinic where the trial sites are located for services relating to injection drug use or other healthcare services. (Bangkok Tenofovir Study)
- Two trials, the CAPRISA 004 and HPTN 035, allow participants who become pregnant to return to product use with a negative pregnancy test. Three trials, the Partners PrEP, FEM PrEP, and MTN-003 allow participants to return to product use with a negative pregnancy test and if they are not breastfeeding. Two trials, the MTN-001 and the Bangkok Tenofovir Study, do not allow participants to return to product after removal from product after a positive pregnancy. The key informant for the MTN-001 trial explained that participants who become pregnant are permanently discontinued from product use due to the short length of the study. The protocol explains that study duration is expected to be a total of a minimum of one year, including study follow up (MTN-001 protocol). She explained that most participants will continue pregnancy and therefore will not have time to return to product anyway. Also, the key informant explained that if a participant falls pregnant, they were clearly not compliant with contraceptive requirements, so more likely to get pregnant again. (MTN-001) The Bangkok Tenofovir key informant explained that the decision to permanently discontinue product for participants who become pregnant was based on concerns about induced abortions (abortions are illegal in Thailand). He explained that "In Thailand abortion is illegal so we didn't want to place a woman in a situation where you could look at the trial and kind of suspect that maybe we were encouraging women to end pregnancy in order to get back into the trial." (Bangkok Tenofovir Study)
- All seven trials refer participants who become pregnant to antenatal care. One trial, Partners PrEP, indicates in the protocol that participants will either receive antenatal care at the study site or be referred for such care. (Partners PrEP protocol). The MTN-001 and

MTN-003 protocols specifically state that sites will not be responsible for paying for pregnancy-related care (MTN-001 and MTN-003 protocols).

- One trial, the MTN-001, states in the study protocol that study staff will talk to the participant about their choices if they become pregnant and can provide information about termination of pregnancy as part of counseling. This is the only study protocol out of the seven that mentions pregnancy options discussions or counseling. (MTN-001 protocol, pg 130). Key informants for five trials discussed that their studies do not discuss pregnancy options with participants who become pregnant. The CAPRISA 004 trial key informant explained that termination is legal in South Africa and available at no cost for women. She explained that participants who become pregnant are counseled in terms of implications for study participation, procedures and institution of product hold, but that there is not discussion of pregnancy options counseling. (CAPRISA 004 email). The Fem Prep trial provided information explaining that because they are funded by USAID, "options are limited in terms of pregnancy options counseling at this time" (email communication with Associate Scientist II, FHI). The key informant for the Bangkok Tenofovir study explained that "official options are limited and we conduct study in government run clinics." (Bangkok Tenofovir Study email). The Partners PrEP protocol states that "research staff will have no part in any decisions related to the timing, method, or procedures related to potential pregnancy termination." (Partners PrEP protocol, pg 68) The HPTN 035 and MTN-003 key informant explained that "It's a very delicate situation. At all of the HPTN 035 sites, elective abortion is illegal except in South Africa. So, you know, the people who work there know the best how to navigate their own local legal requirements. But it's a very taboo topic. So, especially outside of South Africa, it would be pretty unusual for a member of the study team to take that on." The key informant continued to explain that women find ways to induce abortion themselves and she assumes that some of the pregnancy outcomes recorded as spontaneous abortions were really induced abortions. She said that trials "should at least put the issues squarely on the table . . . and say this is going to come up, how are you planning to handle it? At least have a conversation about it and let the sites kind of share and benefit from each others' experience." (HPTN 035)
- A few trials discussed some challenges related to removal of study product when participants test positive for pregnancy. The MTN-001 key informant explained that some participants have misconceptions about what to expect when taken off product regarding compensation if they are no longer using the study product. Also there is concern that participants may not see the need of continuing in study follow up if they are no longer receiving the study product. She explained that the sites are strongly advised to counsel participants about the importance of continued follow up and compensation. (MTN-001). The key informant from the MTN-003 discussed the challenges of needing to educate women and communicate clearly the need to stay off product when they are pregnant. She explained that they don't want women to get pregnant and feel like they are missing out on a benefit because they no longer are getting the product and somehow try to restart product while pregnant. She emphasized the challenge of really providing quality and standardized information and clearly communicating the risks and benefits to the participants and making sure the message is complete. (MTN-003)

Pregnancy testing:

- All seven trials conduct pregnancy testing at the scheduled visits, usually occurring every month, and more frequently if there is indication to do so. The MTN-001 trial has scheduled visits more frequently than monthly, so pregnancy tests are done at every visit at least every three weeks.
- A few trials shared concerns and challenges they had or anticipate to have with pregnancy testing. One issue raised by informants for two trials was the issue of chemical pregnancies. The key informant for the Partners PrEP trial said that a concern is high rates of chemical pregnancies from frequent pregnancy testing. The trial is "expecting to see a lot of positive pregnancy tests, with many fewer clinical pregnancies." (Partners PrEP). The key informant further explained that there has been a lot of discussion on this issue outside of the protocol and there are many different avenues used for continuation of that discussion. He mentioned that there has been training at the site level and at cross-team workshops, and over email and blog communications about "how the site staff [is] to react to that, what are the procedural effects, what are the counseling effects, and what are the discussions with IRBs and with communities about that." (Partners PrEP). The key informant for the Fem Prep trial explained that the trial hasn't started yet, but "from experience and the literature, a problem is chemical pregnancies and taking women off product due to that." (Fem Prep) The key informant for the HPTN 035 discussed one challenge of requiring pregnancy testing each month even when it was known that participants were pregnant. She explained that this practice made sense early in pregnancy because a lot of pregnancies were detected very early on and it was important to continue testing in order to detect if a woman who tested positive possibly miscarried without knowing it. However, it became challenging late in pregnancy to continue testing for the staff and the participant when the participant was clearly pregnant. (HPTN 035) The key informant for the MTN-001 trial expressed the same challenge and explained that investigators are reluctant to do a pregnancy test when they know the test will be positive. (MTN-001)
- When the trials were asked the issue of product use and possible misconceptions about spontaneous abortions (aka miscarriages), a few key informants shared their thoughts. The key informant for the CAPRISA 004 trial indicated that the trial has investigated the issue of misconceptions of participants possibly linking product use with spontaneous abortion, and found that "from participants' point of view there have not been concerns." She further clarified that any comments are based on very few pregnancies that have occurred during the trial so far. (CAPRISA 004) The key informant for the MTN- 001 trial stated that "it maybe has been said, but it has not been an issue or a community problem" for the trial. (MTN-001) The key informant for the Bangkok Tenofovir Study said that "as far as spontaneous abortions and miscarriages related to study drug, [this] has not come up as an issue." (Bangkok Tenofovir Study) The key informant for the Fem Prep trial responded that there are always a lot of things linked to product use, the worst is linking product use with becoming HIV infected. She further added that she "would not say, in the trials I've done, that linking spontaneous abortion to product use is any bigger concern than any other concern related to product use." (Fem Prep). The key informant for the MTN-003 trial said that they have not looked into that issue, but that "it's a really good question". (MTN-003) The key informant for the HPTN 035 trial stated that she "can't recall any specific instance where we were told about an issue or a

problem with that." (HPTN 035) The key informant for the Partners PrEP trial explained that there has been a lot of discussion on this issue outside of the protocol and there are many different avenues used for continuation of that discussion. He mentioned that there has been training at the site level and at cross-team workshops, and over email and blog communications about "how the site staff [is] to react to that, what are the procedural effects, what are the counseling effects, and what are the discussions with IRBs and with communities about that." (Partners PrEP).

Pregnancy tracking and monitoring:

- All seven trials track and record pregnancy outcomes for participants who become pregnant during trials. The CAPRISA 004 study tracks and records pregnancy outcomes as one of its secondary endpoints, and assesses outcomes in the following categories: induced abortion; spontaneous abortion; stillbirth; live birth with a congenital anomaly; or live birth without a congenital anomaly. (CAPRISA 004 protocol, pg. 32). The Bangkok Tenofovir Study asks for consent from women who become pregnant during trial to allow clinical staff to review the medical record of delivery to assess maternal and newborn health. The study then reports pregnancy data and pregnancy outcomes to the Antiretroviral Pregnancy Registry (Bangkok Tenofovir Study, pg. 29). The MTN-001 key informant explained that all pregnancies will be followed to outcome. Any adverse events (AEs), such as fetal loss, congenital abnormalities, and birth defects are reported. (MTN-001 protocol, pg.68) The HPTN 035 key informant explained that pregnancy outcomes and birth outcomes are recorded. (HTPN 035)
- One trial, the Partners PrEP trial, follows the infant for one year. One of the secondary objectives in the Partners PrEP trial is "to assess the effect of TDF and FTC/TDF chemoprophylaxis on the rate of congenital abnormalities and growth among infants born to HIV-1 uninfected female participants who become pregnant during the study." (Partners PrEP protocol, pg. 16). The protocol states that "For pregnancies that go to term, follow-up of infants exposed to study medication will be conducted over the first year of life." (Partners PrEP trial, pg. 68) The key informant for the Fem Prep trial indicated that infants are only followed past birth if there are any abnormal test results. (Fem Prep). The protocol explains that "If an abnormal result was obtained, the child will receive appropriate care and will be monitored as needed. For infants with abnormal lab results, a second visit will occur at age 3 months." (Fem Prep protocol, pg. 55) The Fem Prep trial reports the pregnancy outcome to the Gilead Sciences' Antiretroviral Pregnancy Registry. (Fem Prep protocol, pg. 55.). The key informant for CAPRISA 004 stated that they "do not have any plans to be tracking infants" (CAPPRISA 004). The MTN-003 study indicates that women who become pregnant during the study may be "offered participation in MTN-016, the Prevention Agent Pregnancy Exposure Registry. This registry study is anticipated to capture pregnancy outcomes as well as infant health information, (including growth and development), to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy." (MTN-003 protocol, pg. 82). The HPTN 035 key informant explained that the trial collects birth outcomes and would report any congenital abnormalities found at time of delivery." (HPTN 035)
- A few participants discussed some challenges around tracking and monitoring pregnancies. The key informant for the Fem Prep trial stated that "retention is always a problem in the big trials, so definitely if women are beyond the normal follow up of the

trial, to contact them to get data is a challenge in itself. We have a system to follow up with pregnancy, but it is a challenge." (Fem Prep) The key informant for MTN-003 also indicated that a concern with tracking and monitoring is that "some populations are fairly stable, and some are more mobile than others." (MTN-003) One of the key informants from the CAPRISA 004 trial explained their tracking system in more detail. She explained that the homes of participants do not have numbers, so in order to track outcomes, including pregnancy outcomes, the trial does something called "participant mapping". She explained that at time of enrollment the participants draw a map of how to get to their homes because the homes do not have numbers. (CAPRISA 004)

2. Contraceptive Issues: Sub-themes

Enrollment exclusion/inclusion criteria concerning contraception:

- Four trials require participants to use an effective, non-barrier contraceptive method to enroll. The reasons behind this requirement provided by the key informants was that these methods are more effective at preventing pregnancy, and trials want to prevent pregnancy for two primary reasons: (1) for safety reasons because products have not been tested in pregnancy; and (2) to prevent loss of follow up time due to pregnancy. A key informant from the CAPRISA 004 trial explained that 95% of participants in the trial are already on an effective contraceptive method, primarily injectables, because they recruit from family planning clinics and "these women have already made a choice to be on a contraceptive" (CAPRISA 004). One trial, the Bangkok Tenofovir Study, requires use of an effective contraceptive method, and includes barrier methods in this requirement. The key informant for this trial explained that they do not require only non-barrier methods because they "want women to choose a method they are comfortable using and will use consistently, so if they will use condoms consistently that's okay." (Bangkok Tenofovir Study) Two trials, the Partners PrEP and HPTN 035 trials, do not have any contraceptive method requirement for enrollment. The key informant for the Partners PrEP trial explained that the reason for not requiring that participants use an effective method of contraception was based on reasons of generalizability. One key informant for this trial explained that contraceptive use by the study population, HIV discordant couples, "is low in stable partnerships for lots of reasons, and we didn't want to require it so that the results of our study were that much more generalizable from the study at the end." (Partners PrEP) Another key informant for this trial explained that the decision to not require contraception was based on generalizability but also feasibility issues. This key informant mentioned that the stable discordant couples in the study often want to have children, and it would have "made it very challenging to enroll HIV discordant couples where you have all these other biomedical factors that you have to consider as well as adding that behavioral one" (Partners PrEP). The key informant for the HPTN 035 trial explained that the rationale behind not requiring contraceptive use to enroll was two fold: First, she explained that not requiring contraception "related to the fact that the two products we were studying are not known to be systemically absorbed. So they wouldn't be expected to have any systemic effects, like through the bloodstream to the fetus if the women did become pregnant." She explained that the second reason was to "avoid enrolling more selective populations." She explained that they wanted a broader sample and didn't want to limit their sample to women who would use a non-barrier method of contraception. (HPTN 035)

Provision of contraception:

- All seven trials have onsite provision of contraception free of charge at all sites. All sites provide hormonal birth control pills and injections. Some sites in the Partners PrEP trial are capable of inserting IUDs and implants and are working toward capacity to do this at other sites, but this is not common across all trials. Variability exists across trials and sites as far as which methods are available on site beyond birth control pills and injectables.
- Key informants for seven trials were able to provide information on the availability of emergency contraception (EC). The CAPRISA 004 trial's Manual of Procedures (MOPs) states that EC methods should "always be available and in stock at all health facilities and hence at all CAPRISA 004 trial sites" (CAP 004 MOP). The FEM PrEP key informant provided information explaining that the study manual states that emergency contraception should be provided in the case of rape if the participant agrees. It was further explained that "at this time we do not discuss the use of emergency contraception further in the protocol or manual although sites are free to dispense EC under the direction of the study medical doctors where locally available and acceptable" (email correspondence with an Associate Scientist at FHI, 11/13/08). The Bangkok Tenofovir Study key informant explained that EC is not a service provided by the study or drug treatment clinics that serve as the trial sites, but that EC is available over the counter at low cost at pharmacies in Bangkok and women are generally aware of EC. The key informant for the Partners PrEP trial indicated that EC is not a widely adopted method in Africa. The key informant stated that "It's not that we wouldn't offer it, but I just don't think that it is promoted widely or even understood by women as an option" (Partners PrEP). The MTN-001 key informant explained that EC is not offered at trial sites and explained that "EC is not a widely used method worldwide" (MTN-001). The key informant for the HPTN 035 trial said that to the best of her knowledge, EC was not available at trial sites. The key informant for the MTN-003 study did not believe that there is mention of EC in the study protocol. "I don't think that is in the protocol. That has actually not come up in our conversations" (MTN-003) Another key informant for the MTN-003 trial stated that "I don't know the answer to that. We haven't fully explored that issue yet in preparation for 003. I think the first thing we need to do is explore the country practice guidelines. I don't even know how available it is; but certainly anyone with a pack of contraceptive pills could dispense it. But there are legalities and practice guidelines for each of the sites that we need to sort out and figure out what's going to be happening at the sites related to that." (MTN 003)
- All seven sites provide referrals for services off site for contraceptive methods not available on sites, which typically includes IUDs, sterilization, and implants. The trials have different systems set up for these referrals. The Partners PrEP trial key informant explained that sites are usually connected with a clinic next door or down the road. (Partners PrEP) The MTN-001 key informant indicated that the pregnancy management Standard Operating Procedures (SOPs) require documentation prior to study initiation of where each site will refer participants. (MTN 001) The CAPRISA 004 key informant explained that the sites refer participants to a clinic closest to the participant's residence so it is most convenient for them. (CAPRISA 004) The Fem Prep key informant explained that off site clinics and family planning services are not directly linked to a site, but that sites build relationships with these services so they can refer patients to them.

(FEM PrEP) The Thailand Bangkok Tenofovir study key informant explained that most of the sites – which are drug treatment facilities as the population in the trial is injection drug users – are physically connected to a hospital or larger clinic, so the healthcare services, including contraceptive care, are readily available to trial participants. The key informant further explained that the research team for the trial is composed of doctors and nurses from these hospitals and clinics, so there is a very close working relationship between the trial sites and the hospitals and clinics where the sites are located and there is "good communication and overlap" (Bangkok Tenofovir Study). The key informant for the HPTN 035 and MTN 003 explained that trial sites would have a listing of the government family planning services or clinics, and they would ask the participant where she would want to go. She explained that a couple of the sites were actually situated either within, or directly next door, or within a short walk of the largest family planning clinic in the area." (HPTN 035 and MTN 003).

- Six trials said that most contraceptive methods available at sites are available free of charge in public sector facilities, but a few sites mentioned that accessibility varies by site location. The Partners PrEP key informant indicated that the trial would pay if there was an issue with obtaining a contraceptive method not offered on site. (Partners PrEP) The MTN 003/VOICE trial key informant indicated that the study was not able to pay for methods beyond the contraceptive pills or Depo Provera offered on site because the other methods are more expensive, although the trial is seeking additional funding through grants to systematically train each of the sites to provide IUD insertion on site but has not received funding yet. (MTN 003/VOICE)
- Six trials have a system for recording and monitoring use of contraception in chart notes and/or case report forms (CRFs). Some trials have detailed monitoring, such as the CAPRISA 004 which "monitors closely the pattern of use as well as any changes in pattern" of contraceptive use by participants. (CAPRISA 004) The key participant for the HPTN 035 explained that "as part of the standard data collection we were finding out on a monthly basis if they were on a hormonal method. The details of that got updated every month. And then at every quarter there was kind of a standardized behavioral interview that asked about the contraceptive methods they were using. So it was tracked over time." (HPTN 035). One trial, the Bangkok Tenofovir Study, monitors that participants are continually confirming that they are on an effective contraceptive method, but the sites do not record which methods are being used by each participant.
- Challenges around issues of contraception were discussed. The key informant for the CAPRISA 004 trial mentioned that one of the key challenges around contraception is that women on oral contraceptive pills are the ones most likely to fall pregnant (CAPRISA 004). The FEM PrEP key informant indicated that one challenge they are concerned about is that requiring an effective contraceptive method could have a negative impact on participant enrollment (FEM PrEP). The Partners PrEP trial indicated that one challenge for them was the initial decision not to require an effective contraceptive method for enrollment. The key informant explained that "the initial decision was based on trying to reflect HIV discordant couples in our study communities as best as possible in trial population. If this intervention works to prevent HIV, people are definitely going to use it that have the potential to get pregnant." Once that decision was made, the next challenge was from a study conduct point of view to attempt to minimize pregnancies because women must come off of product if they become pregnant. "The challenge is

maintaining interest of participants in initiating contraception." (Partners PrEP) The key informant for the MTN 003/VOICE trial indicated that cost of providing contraception is a challenge. Additionally, cultural issues such as the core values of fertility and reproduction held by many women and their families in the study populations is a challenge when trials require participants to be on contraception to enroll. The key informant explained that "it's a challenge socioculturally . . . you really have to explain what the balances are in terms of benefits and costs." (MTN 003/VOICE) The HPTN 035 key informant explained that a challenge is the pressures and demands on women from partners and family to have babies. She said "there's an expectation that these women are going to be having babies. There's partner pressure, there's family pressure, and sometimes the decision about whether she's going to be using contraception or whether she's expected to produce a child is out of her control. Regardless of what she may want, there are other pressures on her. So that kind of affects her ability to make her own choices and meet with the requirements of the study over time." (HPTN 035) The key informant for the MTN-001 trial explained that the challenges have to do with acceptability of contraception in certain trial populations. The key informant explained that in Africa, "there is misconception that if you are using contraception that later on it may not be as easy to conceive, or that if you use any method that causes any change in your menstrual cycle that this is very harmful for you because you have to menstruate every month." She further explained that there are some sites where "in the population women don't want to admit they are sexually active, so the use of contraception makes this real." She explained that this makes it complicated because participants don't want to go to the doctor and get a prescription. (MTN-001)

Contraceptive counseling:

- Seven trials provide contraceptive counseling on site, with five trials providing contraceptive counseling at each scheduled site visit. The CAPRISA 004 MOPs explain that contraceptive counseling will be done at enrolment and every follow-up visit (CAPRISA 004 MOPs). The protocol for the Partners PrEP and the FEM PrEP trials indicate that contraceptive counseling is done at enrollment at every follow up visit (Partners PrEP protocol; Fem Prep protocol). The MTN-001 protocol states that "study staff will provide contraceptive counseling to enrolled participants as needed throughout the duration of study," but includes contraceptive counseling in the enrollment and follow up visit checklist documents. (MTN-001 Protocol). The MTN 003 key informant explained that contraceptive counseling is required at every scheduled visit and this is stated in the operational materials for the study. (MTN 003) The HPTN 035 key informant explained that contraceptive counseling at study visits "would kind of reassess where they are every month" and would talk about "if they are having any difficulties with the methods, if they want to stay with the method. However, the protocol does not include any discussion of monthly contraceptive counseling. (HPTN 035) The Bangkok Tenofovir Study protocol does not mention contraceptive counseling. The key informant explained that at monthly visits participants are asked if they are doing well with their contraceptive method of choice and if they have any issues they need to discuss, but that there is not a script for this. (Bangkok Tenofovir Study)
- One key informant discussed some of the challenges regarding the provision of contraceptive counseling to participants. The Partners PrEP key informant talked about

the challenge of having one person at each site responsible for oversight of contraceptive counseling. "We've been working to try to get sites – I've gotten this through at most sites – to try to get sites to designate a specific individual who has been trained in family planning counseling to be the person at the sites who is really responsible for making this a priority for that site. Because among the myriad of other things that have to be done for running the trial, someone has to track and to really go through and say for this particular participant, what did you talk about in there, and when she said this, how did you follow it up and why or why not is she on this method? Getting family planning management and counseling to be a priority at the trial sites. Sites are very busy. To do contraceptive counseling and every time to do effective contraceptive counseling is yet another burden on the site staff and participants, too." (Partners PrEP)

- Six trials explained the training provided to counselors for contraceptive counseling. The key informant for the Partners PrEP trial explained that from the coordinating center trial conduct level, they train counselors about the rationale for contraceptive use within the trial and the protocol requirements for onsite provision of contraception and contraceptive counseling at each scheduled visit. This trial has several email groups that are used for case discussions about a lot of different issues. Beyond that, the training definitely operates at the site level. He explained that "each site does contraceptive counseling probably in their own way. My guess is that methods of counseling are probably not identical across each site. Pretty confident saying that most sites have clinicians or nurse counselors who have national level certification in family planning provision." (Partners PrEP) The key informant for the MTN-001 trial explained that training is provided but not by the protocol team. In Africa sites the counselors are certified in family planning. To meet site requirements, they go through a country training program. The study verifies qualifications before activation of a counselor in study. (MTN-001) The key informant for the CAPRISA 004 trial explained that all staff receives study specific training. The staff directly involved in contraceptive provision receives and continues to receive ongoing training on contraceptive counseling. Nurses and clinicians provide counseling at the sites. (CAPRISA 004) The key participant for the FEM PrEP trial explained that training is done for every trial procedure, including contraception counseling. Each trial site has a curriculum for contraceptive training. In addition to site training, counselors are often sent to a contraceptive expert for training. (FEM PrEP) The key informant for the MTN-003 trial explained that there are numerous ways that training happens and they are currently developing a central investigators training for the study. She explained that contraceptive counseling is covered at the central training level and site specific training level because "it's obviously a critical component in making sure women are enrollable and also making sure they are staying on their medication." (MTN-003) Another MTN 003 key informant explained that they "are going to pull together some counseling training module that sort of builds on what we would expect to be in place at the site, but also make it more study specific given that we are requiring contraception. I think we do have to provide some kind of training around that that would be beyond what we thought we needed to do with the HPTN 035 where it wasn't required to use a method."

Overall key challenges regarding pregnancy management and contraceptive care:

Partners PrEP

- Designing trials that acknowledge the importance of fertility in study eligibility and study management
- Getting family planning management and counseling to be a priority in the trial
- Increase use of IUDs, which is one of the best ways to prevent pregnancies, but there are very low rates of IUD use in Africa.

MTN-001

- Education: acceptability of contraception in certain African populations. Misconceptions about changing menstrual cycle, future fertility.
- Cultural norms: participant embarrassment about acknowledging contraceptive use because it confirms that you are sexually active.

CAPRISA-004

- The most pregnancies are occurring among women on birth control pills. Women choosing oral contraception as their contraceptive method and then staying adherent to it.

FEM PREP:

- Recruitment: For many women requiring use of effective contraception will be something they don't accept or their partners don't accept that they be on effective contraception.
- Keeping women on contraception. Once they are in the trial we don't remove them from the trial if they stop using the contraception.

MTN-003:

- Funding: To figure out a way to nest a sub-objective within a study like MTN-003 to look more carefully to see which contraceptive methods women are on and how that might feed into modifying the risk of getting HIV by different treatment arms.
- Funding: Increase the diversity of methods women have access to at trial sites. Increasing IUD use. Need additional funding to cover costs for expansion of methods.

HPTN-003:

- Pressures from family and partners on women to have children. Makes it difficult, especially in a longer study, for women to stay adherent to contraceptive use (especially when user-controlled like birth control pills) and not get pregnant.
- Studies are asking women to do a lot. For example, to take possibly two different pills or insert one applicator of gel everyday, to always use condoms, to maintain birth control use, along with all the counseling messages they are receiving. A challenge is to deliver all those messages in a way that will be most helpful to the participants.
- Dealing with the legalities and taboos around induced abortions.

Bangkok Tenofovir Study:

- It was difficult to increase the number of women enrolling in the study (women account for only 20% of study population).
- Induced abortion was a challenging theme. In Thailand abortion is illegal, so the trial didn't want anyone to suspect that the trial was in any way encouraging or motivating women to end pregnancy in order to return to the trial. A decision was made to discontinue permanently from the trial any woman becoming pregnant during the trial duration.

B. Quantitative Survey

Background Information of Professionals

Table 1 provides descriptive background information for the total sample of professionals working in the HIV field. The three primary fields of work are social and behavioral research (27.0%), advocacy work (22.9%), and medical research (18.8%). Just under half of the sample reported they work in a non-governmental organization (NGO) (47.1%), with just over one quarter in a university setting (27.9%). The majority of professionals reported they have a MPH (46.0%) and/or PhD (34.9%). The majority of the sample is involved in work in the North America region (63.0%) and/or sub-Saharan Africa region (43.0%), with one-quarter of respondents reporting they work in a region of Asia (25.0%). **Table 1.1** provides descriptive background information for the sample of professionals who work in HIV prevention trials and shows professionals working in HIV prevention trials work primarily in medical research (29.6%) and/or social & behavioral research (20.4%), and/or biomedical research (20.4%) and hold a MPH (44.4%) and/or MD (44.4%). **Table 1.2** provides descriptive background information for the professionals that do not work in HIV prevention trials, and shows that this sample works primarily in advocacy (39.0%) and/or social & behavioral research (36.6%) and holds a MPH (48.0%) and/or PhD (44.0%).

Professionals' Perceptions Related to Contraceptive Issues in HIV Prevention Trials

Table 2 provides descriptive information on the perceptions of the total sample related to contraceptive issues in HIV prevention trials. The results show that over half (56.8%) of the total sample reported they strongly disagree/disagree that a non-barrier form of contraception should be required for all participants in trials. Nearly 95% of respondents agree/strongly agree that a non-barrier form of contraception should be offered to participants at trials sites. The minority of respondents (28.0%) agree/strongly agree that participants should be denied participation in a

trial if they refuse to use a non-barrier contraceptive method. Nearly 85% of respondents agree/strongly agree that emergency contraception (EC) should be integrated into the contraceptive services offered to trial participants, and almost 90% agree/strongly agree that EC should be offered to participants at the study sites, opposed to through referrals to outside services. The majority of respondents (87.5%) strongly disagree/disagree that participants should be required to use a long-term method of contraception (Norplant or IUD), while approximately the same percentage (86.3%) agree/strongly agree that participants should be offered these long-term methods of contraception. Most respondents (94.5%) agree/strongly agree that providing on-site contraceptive services and counseling to trial participants is a viable way to improve preventive care practices. Approximately 70% of the sample agrees/strongly agrees that all trial sites should be linked or co-located with a family planning service or clinic.

Table 2.1 provides descriptive information on perceptions related to contraceptive issues for the sample involved in HIV prevention trials and **Table 2.2** provides descriptive information for the sample not involved in HIV prevention trials. These two samples were compared in order to see if perceptions of professionals working in the HIV field on issues of pregnancy management and contraceptive care varied based on involvement in clinical trials. The results for both samples are similar to the results for the total sample, with the exception of the results for statement 8. While 40% of the sample that is involved in work on trials agrees/strongly agrees with the statement (participants should be denied participation in a trial if they refuse to use a non-barrier contraceptive method), 14.7% of the sample not involved in HIV prevention trials responded the same way.

Professionals' Perceptions Related to Pregnancy Issues in HIV Prevention Trials

Table 3 provides descriptive information for the perceptions of the total sample pertaining to pregnancy issues in HIV prevention trials. Over 90% of total sample agree/strongly agree that a trial should be responsible for referring a woman who becomes pregnant during the trial to antenatal care services. The majority of respondents (85.3%) also agree/strongly agree that a trial should provide pregnancy options (a term used to describe the different choices a woman has when she learns she is pregnant) counseling to a woman who becomes pregnant during a trial. Approximately 88% agree/strongly agree that all trials should monitor pregnancy and birth outcomes of participants who become pregnant during the trial. Less than half of respondents (41.2%) agree/strongly agree that pregnancy testing during trials should be conducted less frequently than once per month to help reduce detection of chemical or false pregnancies, while 71.0% agree/strongly agree that pregnancy testing should be conducted once per month to ensure that pregnancy is detected as soon as possible. The majority (88.7%) agree/strongly agree that preclinical and clinical safety and toxicity studies of microbicide candidate products should include studies of reproductive toxicity, teratogenicity, and carcinogenicity so that female participants who do become pregnant during the efficacy trials of these candidate products could possibly remain on product throughout the trial.

Table 3.1 provides results for the sample involved in HIV prevention trials and **Table 3.2** provides results for the sample not involved in HIV prevention trials pertaining to issues of pregnancy. These two samples were compared in order to see if perceptions of professionals working in the HIV field on issues of pregnancy management and contraceptive care varied based on involvement in clinical trials. The results for both samples are similar to the results for the total sample, with the exception of the results for statement 19 and statement 20. For

statement 19, while 61.1% of the sample involved in work on trials agree/strongly agree with the statement (pregnancy testing during trials should be done at least once a month to ensure that pregnancy is detected as soon as possible), 80.0% of the sample not involved in trials answered the same way. For statement 20, while 95.0% of the sample involved in work on trials agree/strongly agree with the statement (preclinical and clinical safety and toxicity studies of microbicide candidate products should include studies of reproductive toxicity, teratogenicity, and carcinogenicity so that female participants who do become pregnant during the efficacy trials of these candidate products could possibly remain on product throughout trial), 80.0% of the sample not involved in work on trials answered the same way.

Differences in Professionals' Perceptions on Specific Statements by Sample

Figure 1 shows the percent of the sample involved in work on clinical HIV prevention trials (n=56) and percent of the sample not involved in work on clinical HIV prevention trials (n=47) who agree/strongly agree with statement 8. **Figure 2** shows the percent of sample involved in work on clinical HIV prevention trials (n=56) and percent of the sample not involved in work on clinical HIV prevention trials (n=47) who agree/strongly agree with statement 19. **Figure 3** shows the percent of the sample involved in work on clinical HIV prevention trials (n=56) and percent of the sample not involved in work on clinical HIV prevention trials (n=47) who agree/strongly agree with statement 20.

V. Discussion

Key Informant Interviews

Most of the microbicide and PrEP trials included in the key informant surveys have made similar overall decisions concerning pregnancy management and contraceptive care practices and services. Ethical and regulatory standards play a role in influencing many of the practices and services that are common across trials. For example, all trials exclude pregnant women from

enrolling in the trial and immediately discontinue product use for women who test positive for pregnancy during the follow up period. Other practices such as performing pregnancy tests at each scheduled visit are shared by all trials in order to remove women from study product as soon as possible due to safety concerns. In addition, all trials are attempting to prevent pregnancies during trials by excluding women who indicate that they plan to get pregnant during study duration. All trials approach pregnancy prevention through direct on-site provision of effective contraceptive methods, typically hormonal pills and shots, and referrals out to public family planning services and clinics for contraceptive methods not available at the trial sites. In addition, all trials attempt to provide care that will be beneficial to study participants in the case that pregnancies still occur. For example, trials refer participants who test positive for pregnancy to medical care or antenatal care services and most trials continue all study-related services that are appropriate during pregnancy. All trials also attempt to track pregnancy outcomes of participants who become pregnant during the trial.

Nonetheless, variations for practices and services relating to pregnancy management and contraceptive care do exist across trials. The key variations warranting further discussion are related to the following practices: requirements for contraceptive use; emergency contraception; pregnancy options counseling; contraceptive counseling; and overall challenges facing trials.

For example, five trials require participants to use an effective method of contraception while two do not. The key informant interviews provided insight into the different decisions that trials made concerning this issue. Most of the PrEP trials require participants to us an effective non-barrier method of contraception as an inclusion criteria because these methods have been shown to be most effective in preventing pregnancy. On the other hand, one PrEP trial, although equally concerned with preventing pregnancies, does not require contraceptive use as an

inclusion criterion. This decision was based on concerns of generalizability of study results and feasibility of enrolling participants if non-barrier methods of contraception were required as an inclusion criterion. In addition one of the microbicide trials did not require participants to use an effective method of contraception. The rationale behind this decision was two-fold. First, the two candidate products being tested in the study are not known to be systemically absorbed and, therefore, safety concerns were not as heightened as with products that show systemic absorption. Second, the trial wanted to avoid enrolling a more selective population by requiring women to use an effective contraceptive method.

Another variation seen across trials relates to the exclusion of breastfeeding participants. While all five PrEP trials exclude breastfeeding women, neither of the two microbicide trials have this exclusion. The reason for exclusion of breastfeeding women in the PrEP trials is based on the safety data for the candidate products being tested. The PrEP trials involve oral ARVs, such as tenofovir (TDF) and emtricitabine (FTC), for which the effects on breast milk are unknown. Interestingly, one of the microbicide trials is testing tenofovir in the gel form and does not exclude breastfeeding women from the trial based on the rationale that safety data from other trials shows that the product remains mostly in the genital track without systematic absorption. However, two of the PrEP trials that are also testing tenofovir gel in one of the study arms in their trials do exclude breastfeeding women from participating and from returning to product after pregnancy until no longer breastfeeding. These trials explain in their protocols that the effects of oral tenofovir and tenofovir gel on breast milk are not known. These two opposing practices among trials testing tenofovir gel demonstrate that trials have made different decisions about the use of this candidate product by breastfeeding women.

The availability of emergency contraception (EC) from trials is another variation worthy of discussion. While one trial includes in its procedural documents a statement that EC methods should always be available and in stock at all trial sites, another trial provides EC in the case of rape if the participants agree, but does not discuss EC beyond that in the protocol or manual. One trial explained that EC is not available at study sites, but it is available over the counter at low cost and most women are generally aware of it. The other four studies either discussed how EC is not widely available or accepted in the areas where their sites are located, primarily in Africa, or expressed that they have not yet looked into the issue of availability or acceptance around their trial sites and have not yet made any decision on the practices around this method. The variation among trials for EC practices demonstrates that certain practices and services in trials are strongly influenced by distinct local circumstances where the trials are taking place. Another example of a practice that is strongly influenced by local circumstances is the practice of pregnancy options counseling. While one trial offers pregnancy options counseling and can even discuss options for pregnancy termination, the other trials are limited by regulations and cultural beliefs relating to what is acceptable to discuss officially with patients related to pregnancy options, particularly relating to pregnancy termination.

Yet another area of variation worth further discussion is the provision of contraceptive counseling. Although the trials do not appear to vary on the surface as they all provide contraceptive counseling to study participants, the approaches that the trials take for provision of contraceptive counseling do appear to vary. On one end of the spectrum, five trials clearly describe that contraceptive counseling is to be provided at enrollment and at every follow-up visit. All five of these trials have requirements for use of effective contraceptive methods. On the other end of the spectrum, two trials do not mention contraceptive counseling in the

protocols, although the key informant explained that counselors do discuss contraceptive issues with participants at visits and reassess contraceptive use, although there are not any scripts for this practice. One of these trials requires an effective method of contraceptive use while the other does not.

The training for study counselors providing contraceptive counseling to participants is an interesting area of discussion. The key informants for most trials were able to say that counselors have national level certification in family planning, and that site staff receive training for contraceptive care practices. Most sites indicated that counselors providing contraceptive counseling receive training on numerous levels and through different methods. However, one key informant stated that each site in the trial probably does contraceptive counseling in its own way. One of the key informants for a different trial mentioned that they are working on developing some counseling training modules and attempting to make them more study specific given that contraception is required in the study. Although all key informants indicated that study counselors receive training on contraceptive counseling and are fully qualified, further examination into this issue is needed to fully understand the training provided to study counselors and the implications that counselor training has on the quality of contraceptive counseling and care provided to study participants.

The challenges that face trials around issues of pregnancy management and contraceptive care vary based on many factors, such as the study product under investigation, the population enrolling in the study, the length of the study, site capacity, funding, and the cultural and legal context where the trial is taking place. Many of the challenges discussed by the key informants related to cultural norms and beliefs of the trial populations. For example, numerous key informants discussed family or partner expectations that are placed on women to bear children,

and the importance that fertility holds in these cultures. This is especially challenging because the women enrolling in HIV prevention trials are typically young women of reproductive age. Misconceptions held by women in certain cultures about specific contraceptive methods was another challenge, as were issues of embarrassment related to contraceptive use because use of a contraceptive method acknowledges sexual activity. Trials are challenged by these cultural beliefs which can impact enrollment as well as contraceptive uptake and adherence by trial participants.

Increasing the availability of more diverse methods of contraception at trial sites was another challenge. As knowledge and acceptability of contraceptive methods varies by region and culture, some of the long term methods of contraception that are highly effective, such as IUDs, are not commonly used by women in certain regions of the world. This makes it difficult, especially in the short term, to supply these methods and increase uptake among trial participants. Funding and resource limitations are also challenges for the expansion of contraceptive methods and overall dictate how much a trial can implement. One key informant mentioned that it would be useful to nest other sub-objectives within a trial to look more carefully to see which contraceptive methods women are on and how that might feed into modifying the risk of getting HIV by different treatment arms, but explained that this was not possible to do because of funding restrictions. (MTN-003)

Overall, one of the key informants summed up the challenges faced by HIV prevention trials with respect to pregnancy management and contraceptive care by stating that a main challenge is merely "getting family planning management and counseling to be a priority in a the trial." (Partners PrEP)

Survey

Overall, the survey results demonstrate that professionals working in the HIV field are in agreement about most of the contraceptive and pregnancy issues included in the survey statements. There are, however, a few statements to highlight that show a noticeable difference in response between the samples involved in work for HIV prevention trials and those not involved in work in HIV prevention trials.

Contraceptive Issues

The responses for statement 8 show a noticeable difference in percentage between the samples for agreement with the statement. While 40% of the sample that works in HIV prevention trials agrees/strongly agrees with statement 8 – that participants should be denied participation in a trial if they refuse to use a non-barrier contraceptive method – only 14.7% of the sample not involved in HIV prevention trials responded the same way, giving a difference of approximately +25% (Figure 1). Examining the comments provided by respondents for this statement provides some insight into the difference in perspective between the two samples, or at least underscores the complexity of the issue.

The sample that works on HIV prevention trials provided six comments relevant to issues of freedom of choice of participants to make decisions about family planning. One respondent commented that "we should promote as much choice as possible unless the risk is very high." There were also six comments focused on the issue of effective non-barrier methods of contraception being necessary for safety reasons. There was one comment relating to the issue that not all women are able to use non-barrier methods. There were also 3 comments around the issues of high pregnancy rates negatively impacting trial outcomes and the loss of women due to pregnancy being costly to trials. One respondent commented that it "wastes time and money if

they fall pregnant and are not able to use the study product being tested." The issue of loss of follow-up time due to pregnancy was not brought up in any of the comments in the sample of professionals not involved in HIV prevention trials.

The sample not involved in HIV prevention trials provided six comments focused on freedom of choice of participants to make decisions about family planning. Three of the comments focused on the difficulty of requiring non-barrier methods because some women have side effects or adverse reactions to certain non-barrier methods. For example, one respondent commented that "a specific requirement of non-barrier methods . . . may unfairly exclude women who are unable to tolerate these oral contraceptive methods, or for whom they are otherwise contraindicated." Two of the comments focused on the issue of needing effective contraception due to safety issues. One respondent commented that effective contraception may be required when product "effects on pregnancy outcomes and fetal development remains unknown or is already documented to be harmful." There were no comments in this sample pertaining to the issue of loss of follow up time due to pregnancy or how pregnancy can complicate a trial.

The respondents from the two samples clearly have both overlapping and distinct perspectives when it comes to the issue of requiring use of a non-barrier method of contraception during trials. The sample involved in clinical trials focused on four key themes in their comments for statement 8: (1) issues around freedom of choice; (2) issues around safety of the mother and fetus; (3) issues regarding exclusion of women from trials due to adverse reactions or inability to use non-barrier methods of contraception; and (4) methodological issues that may affect the implementation and interpretation of a trial. The sample of professionals not involved in HIV prevention trials primarily focused on three key themes: (1) issues around freedom of choice; (2) issues regarding exclusion of women from trials due to adverse reactions or inability

to use non-barrier methods of contraception; and (3) issues of safety to the women or fetus. While three of the themes overlap, the fourth theme concerning methodological challenges that trials are faced with when pregnancy occurs is absent from the responses of professionals not involved in HIV prevention trials. It is possibly this issue that influences the difference in perspective between these two samples for item number 8 in the survey and may partially account for a larger percentage of the respondents involved in clinical trials agreeing with the statement that participants should be denied participation in trials if they refuse to use a non-barrier method of contraception. Further research into this issue would be necessary to determine if and why professionals in the two samples truly have differing perspectives.

Pregnancy Issues

When the survey sample is broken down into the respondents who work in HIV prevention trials and those who do not work in HIV prevention trials, there are two sets of data to highlight that show noticeable differences between the responses of the samples.

First, while 61.1% of the sample working in clinical trials agrees/strongly agrees with statement 19, that pregnancy testing during trials should be done at least once a month to ensure that pregnancy is detected as soon as possible, 81.3% of the sample not working in clinical trials responded the same, giving a difference of +20.2% (Figure 2). While overall both samples agree with the statement, reviewing the comments provided by respondents from each sample gives insight into a possible explanation for why the difference between the samples may have occurred. The sample involved in trials commented numerous times that it depends, while none of the respondents in the sample not involved in trials commented this way. For example, one respondent from the sample involved in trials commented that "it likely depends on the trial design, study agent/drug/intervention and main outcomes." Another respondent commented that

it “depends on how often they are seen for the trial, what drug/device is being trialed, etc.” And a third respondent stated “depending on the need and risks to the baby.” It is possible that the sample involved in trials did not agree as strongly with the statement as the sample not involved in trials because the professionals working on trials are more familiar with the context of clinical HIV prevention trials from experience and are more aware of the factors that can influence the practices around pregnancy testing in trials, leading to some of their comments indicating that the frequency of pregnancy testing really depends on the particular trial. Further research into this issue is needed to fully understand why the samples had a noticeable difference in response.

Second , 95.0% of the sample working in trials agrees/strongly agrees with statement 20 about preclinical and clinical safety and toxicity studies, while 80% of the sample not working in trials responded the same way, giving a difference of +25.0% (Figure 3). Examination of the comments did not provide any insight into why this difference in response may have occurred between the samples. The comments provided by both samples were fairly lengthy and complex, which may reflect the complexity of this issue in clinical trials. Further research into this area would be necessary to determine if and why professionals in the two samples truly have differing perspectives on this issue.

Comparison of Key Informant Interview and Survey Results

It is interesting to make some preliminary comparisons between the perceptions of professionals discovered in the survey results and the practices occurring in the planned and ongoing microbicide and PrEP trials represented in the key informant interviews. Statement 6 states that non-barrier contraceptive methods should be required for participants in trials. Less than half of the professionals for the total sample, sample working in trials, and sample not working in trials agreed/strongly agreed with the statement. However, of the seven trials

represented in key informant interviews, four of the five PrEP trials and one of the two microbicide trials require non-barrier contraceptive use.

A second comparison worth mention relates to perceptions of professionals and practices in trials for provision of emergency contraception (EC). Over 80% of each the total sample, sample involved in trials, and sample not involved in trials agrees/strongly agrees with statement 10 that emergency contraception should be offered to study participants at the trial site as opposed to through referrals. As discussed above, EC is only available at sites for two trials and the other trials indicated that their trial sites do not offer EC due to the local circumstances influencing availability and acceptability. Nonetheless, this is an area of perceived importance by professionals in the HIV field and important for trials to at least consider and research further to determine if integration of EC into contraceptive services is a feasible option for pregnancy prevention.

A third comparison relates to the provision of pregnancy options counseling at trial sites. The survey results show that over 80% of each the total sample, sample involved in trials, and sample not involved in trials agrees/strongly agrees with statement 16 that all trials should provide pregnancy options counseling (a term used to describe the different choices a woman has when she learns she is pregnant) to a woman who becomes pregnant during the trial. As discussed above, only one of the seven trials includes in its practices discussions of pregnancy options with participants who become pregnant during the trial. The other trials explained that they are restricted by official regulations or the local circumstances from officially discussing pregnancy termination with study participants. Nonetheless, as one key informant mentioned, women find ways to induce abortion themselves if abortion is not legal. The key informant suggested that trials "should at least put the issues squarely on the table . . . and say, this is going

to come up, how are you planning to handle it? At least have a conversation about it and let the sites kind of share and benefit from each others' experience." (HPTN 035) More research is needed to fully understand how trials have dealt with situations in which women induce abortion and how the implications of this can be dealt with by the trial staff, both for the participant's well being and also for data collection and analysis purposes relating to pregnancy management.

VI. Recommendations

- Continue to increase priority for the integration of reproductive and sexual health care, including pregnancy management and contraceptive care, in clinical HIV prevention trials.
- Proactive and thoughtful efforts needed to balance the safety and well-being of participants and their fertility choices with the needs of clinical trials.
- Implement different approaches for measuring pregnancy wantedness and intentions prior to study enrollment
- Expand opportunities for dialogue among professionals working in HIV prevention in order to share knowledge and experiences that could enhance pregnancy management and contraceptive care practices in ongoing and planned clinical HIV prevention trials.
- Continue to work toward diversification of effective contraceptive methods available to trial participants through direct on-site provision in order to provide women with more choices.
- Further research on the quality of contraceptive provision and counseling provided to participants in HIV prevention trials to determine which approaches

are working well, and the sharing of these approaches across clinical HIV prevention trials.

- Invest in the strengthening of contraceptive counseling and pregnancy management training for clinical staff in order to enhance the quality of contraceptive care and counseling provided to study participants.
- Increase discussion regarding pregnancy options counseling, even at site locations where abortion is illegal, so study staff is prepared to deal with this often sensitive issue as appropriately as possible in order to protect the well-being of study participants and the accuracy of data collection.
- Further research on the viability of integrating emergency contraception into contraceptive care practices at trial sites.

APPENDIX

CHART A

MICROBICIDE CANDIDATES IN ONGOING CLINICAL TRIALS

Phase	Candidate Name	MoA	Title of Study	Sponsor	Sites by Country
3	PRO 2000/5 gel	EFI	Efficacy and safety in 0.5% PRO 2000/5 gel for the prevention of vaginally acquired HIV infection (MDP 301)	DFID (Funder), Indeves, MRC	South Africa, Tanzania, Uganda, Zambia
2B	***Tenofovir gel***	***RI***	***Safety and effectiveness study 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 and BufferGel***	***EFI, VDE***	***Safety and effectiveness study of the vaginal microbicides BufferGel and 0.5% PRO 2000/5 Gel 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 to pharmacokinetics study of oral and vaginal preparations of tenofovir (MTN 001)***	***CONRAD, DAIDS/NIAID, Gilead, MTN***	***South Africa, Uganda, United States***

MICROBICIDE CANDIDATES IN PLANNED AND FUNDED CLINICAL TRIALS

Phase	Candidate Name	MoA	Title of Study	Sponsor	Sites by Country
3	ACIDFORM/Amphora	VDE	Trial of the diaphragm with a candidate microbicide to prevent sexually transmitted infections	CDC, CONRAD, NIH	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		
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***	***Sites in Africa TBD***

Definition of acronyms used in this table: Mechanism of Action (MoA); Entry/Fusion Inhibitor (EFI); Replication Inhibitor (RI); and Vaginal Defense Enhancer (VDE).
Italicized/bolded trials highlighted in gray were included in key informant interviews and protocol review discussed in this paper.
SOURCE: Alliance for Microbicide Development. November 2008 Pipeline Update. Available at: http://www.microbicide.org/cs/clinical.

APPENDIX

PrEP CANDIDATES IN ONGOING CLINICAL TRIALS

Phase	Candidate Name	Title of Study	Sponsor	Sites by Country
2	**TDF**	***Adherence to pharmacokinetics study of oral and vaginal preparations of tenofovir (MTN 001)***	***CONRAD, DAIDS/NIAID, Gilead, MTN***	***South Africa, Uganda, United States***
3	***TDF; TDF + FTC***	***Partners PrEP: Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition Within HIV-1 Discordant Couples***	***BMGF***	***Kenya, Uganda***
3	***TDF***	***Study of the Safety and Efficacy of Daily Tenofovir to Prevent HIV Infection Among Injection Drug Users in Bangkok, Thailand (Bangkok Tenofovir Study)***	***CDC***	***Thailand***
3	TDF + FTC	TDF2	CDC	Botswana

PrEP CANDIDATES IN PLANNED CLINICAL TRIALS

Phase	Candidate Name	Title of Study	Sponsor	Sites by Country
2/2B	***TDF; TDF + FTC***	***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***	***Sites in Africa TBD***
3	***TDF + FTC***	***FEM PrEP (Truvada): Study to Assess the Role of Truvada® in Preventing HIV Acquisition in Women***	***FHI, USAID***	***Kenya, Malawi, South Africa, Tanzania***

Definition of acronyms used in this table: Oral tenofovir disoproxil fumarate (TDF); *emitricitabine (FTC)*
Italicized/bolded trials were included in key informant interviews and/or protocol review discussed in this paper.
SOURCE: PrEP Watch. Ongoing and Planned PrEP Trials as of July 2008. Available at: http://www.prepwatch.org/pdf/Trials/PrEP_trials_table.pdf.

APPENDIX

CHART B (*see separate attachment*)

APPENDIX

Chart C: Summary of PrEP and microbicide trials meeting criteria related to pregnancy management and contraceptive care

Criteria	# of Prep Trials (n=5)	# of Microbicide Trials (n=2)
Exclude pregnant women	5	2
Exclude breastfeeding women	5	0
Exclude women w/pregnancy intentions	5	2
Require effective contraception	4	1
On site provision of contraception	5	2
Refer out for contraception not available on site	5	2
Record use of contraceptive methods by participants	4	2
Emergency contraception available on site	1	1
Provision of contraceptive counseling on site	5	2
Pregnancy testing at least once a month	5	2
Discontinue product use with positive pregnancy test	5	2
Continue most other study services during pregnancy	4	2
Permit participant to return to product use with negative pregnancy test	0	2
Permit participant to return to product use with negative pregnancy test and no longer breastfeeding	3	0
Refer participants testing positive for pregnancy to antenatal care	5	2
Provide participants testing positive for pregnancy with pregnancy options counseling	0	1
Track pregnancy outcomes	5	2
Track all infant past birth outcomes	1	0
Track infant past birth outcome if abnormalities at birth	1	0

APPENDIX

Table 1: Background for Total Sample (n=106)

Area of HIV Work	% (n) n=96
Advocacy	**22.9 (22)**
Policy	8.3 (8)
Ethics	00.0 (0)
Patient Care	8.3 (8)
Medical Research	18.8 (18)
Social & Beh Research	**27.0 (26)**
Biomedical Research	12.5 (12)
Pharmaceutical Research	2.1 (2)

Type of Org.	% (n) n=104
Govt	20.2 (21)
NGO	**47.1 (49)**
Private	4.8 (5)
Univ.	**27.9 (29)**

Prof Degree(s)	% (n) n=63
DrPH	6.3 (4)
JD	0.0 (0)
MD	31.7 (20)
MPH	**46.0 (29)**
MSW	4.8 (3)
PhD	**34.9 (22)**

Region of Work	% (n) n=100
North Am.	**63.0 (53)**
Latin Am.	8.0 (8)
E. Europe	4.9 (4)
W. Europe	7.0 (7)
N. Africa	1.0 (1)
Sub-Sah. Africa	**43.0 (43)**
S. Asia	9.0 (9)
S-E Asia	14.0 (14)
N-E Asia	2.0 (2)
Pacific Region	2.0 (2)
Mediterranean Region	0.0 (0)

Involved in HIV Prevention Trials	% (n) n=103
Yes	**54.4 (56)**
No	45.6 (47)

APPENDIX

Table 1.1: Background for Sample Involved in HIV Prevention Trials (n = 56)

Area of HIV Work	% (n) n=54
Advocacy	11.1 (6)
Policy	9.3 (5)
Ethics	00.0 (0)
Patient Care	5.6 (3)
Medical Research	**29.6 (16)**
Social & Beh Research	**20.4 (11)**
Biomedical Research	20.4 (11)
Pharmaceutical Research	3.7 (2)

Type of Org.	% (n) n=55
Govt	25.5 (14)
NGO	**38.2 (21)**
Private	3.6 (2)
Univ.	**32.7 (18)**

Prof Degree(s)	% (n) n=36
DrPH	2.8 (1)
JD	0.0 (0)
MD	**44.4 (16)**
MPH	**44.4 (16)**
MSW	2.8 (1)
PhD	30.6 (11)

Region of Work	% (n) N=54
North Am.	**61.1 (33)**
Latin Am.	11.1 (6)
E. Europe	1.9 (1)
W. Europe	5.6 (3)
N. Africa	1.9 (1)
Sub-Sah. Africa	**55.6 (30)**
S. Asia	11.1 (6)
S-E Asia	16.7 (9
N-E Asia	1.9 (1)
Pacific Region	1.9 (1)
Mediterranean Region	0.0 (0)

Involved in Clinical Trials	% (n) n=56
Yes	**100.0 (56)**
No	0.0 (0)

APPENDIX

Table 1.2: Background for Sample Not Involved in HIV Prevention Trials (n = 47)

Area of HIV Work	% (n) n=41
Advocacy	**39.0 (16)**
Policy	7.3 (3)
Ethics	00.0 (0)
Patient Care	12.2 (5)
Medical Research	2.4 (1)
Social & Beh Research	**36.6 (15)**
Biomedical Research	2.4 (1)
Pharmaceutical Research	0.0 (0)

Type of Org.	% (n) n=47
Govt	14.9 (7
NGO	**57.4 (27)**
Private	4.3 (2)
Univ.	**23.4 (11)**

Prof Degree(s)	% (n) n=25
DrPH	4.0 (1)
JD	0.0 (0)
MD	16.0 (4)
MPH	**48.0 (12)**
MSW	8.0 (2)
PhD	**44.0 (11)**

Region of Work	% (n) N=45
North Am.	**66.7 (30)**
Latin Am.	4.4 (2)
E. Europe	6.7 (3)
W. Europe	8.9 (4)
N. Africa	0.1 (0)
Sub-Sah. Africa	**26.7 (12)**
S. Asia	6.7 (3)
S-E Asia	8.9 (4)
N-E Asia	2.2 (1)
Pacific Region	2.2 (1)
Mediterranean Region	0.0 (0)

Involved in Clinical Trials	% (n) n=47
Yes	0.0 (0)
No	**100.0 (47)**

APPENDIX

Table 2: Total Sample Perceptions Related to Contraceptive Issues (n = 106)
(See Figure 4 for results displayed in a bar graph)

Statement	Strongly Disagree and Disagree % (n)	Agree and Strongly Agree % (n)	# of comments (n)
6. Non-barrier contraceptive methods should be required for participants in trials.	**56.8 (42)**	43.2 (32)	46 (74)
7. Non-barrier contraceptive methods should be offered to participants at all trials sites.	5.3 (4)	**94.6 (71)**	**40 (75)**
8. Participants should be denied participation in a trial if they refuse to use a non-barrier contraceptive method.	**72.0 (54)**	28.0 (21)	39 (75)
9. Emergency Contraception (EC) should be integrated into contraceptive services offered to study participants.	12.2 (9)	**87.8 (65)**	**33 (74)**
10. Emergency Contraception (EC) should be offered to study participants at the trial site (as opposed to through referrals).	16.4 (12)	**83.5 (61)**	**33 (73)**
11.All trial participants should be required to use a long-term method of contraception (Norplant or IUD)	**87.5 (63)**	12.5 (9)	39 (72)
12.All trial participants should be offered a long-term method of contraception (Norplant or IUD)	13.7 (10)	**86.3 (63)**	**35 (73)**
13. Providing on-site contraceptive services and counseling to trial participants is a viable way to improve preventive care practices.	5.4 (4)	**94.5 (69)**	**26 (73)**
14.All trial sites should be linked or co-located with a family planning service or clinic	29.0 (22)	**71.0 (54)**	**36 (74)**

Note: The terms “trial” and “trials” refer to HIV prevention clinical trials in phase II or phase III, specifically microbicide and pre-exposure prophylaxis (PrEP) trials, involving female study participants.

APPENDIX

Table 2.1: Sample Involved in HIV Prevention Trials Perceptions Related to Contraceptive Issues (n = 56)

Statement	Strongly Disagree and Disagree % (n)	Agree and Strongly Agree % (n)
6. Non-barrier contraceptive methods should be required for participants in trials.	**55.0 (22)**	45.0 (18)
7. Non-barrier contraceptive methods should be offered to participants at all trials sites.	5.2 (2)	**94.8 (37)**
8. Participants should be denied participation in a trial if they refuse to use a non-barrier contraceptive method.	**60.0 (24)**	40.0 (16)
9. Emergency Contraception (EC) should be integrated into contraceptive services offered to study participants.	15.4 (6)	**84.6 (33)**
10. Emergency Contraception (EC) should be offered to study participants at the trial site (as opposed to through referrals).	20.5 (8)	**79.5 (31)**
11.All trial participants should be required to use a long-term method of contraception (Norplant or IUD)	**89.8 (35)**	10.3 (4)
12.All trial participants should be offered a long-term method of contraception (Norplant or IUD)	18.6 (7)	**81.5 (31)**
13. Providing on-site contraceptive services and counseling to trial participants is a viable way to improve preventive care practices.	2.6 (1)	**97.3 (37)**
14.All trial sites should be linked or co-located with a family planning service or clinic	33.3 (14)	**66.7 (28)**

Note: The terms “trial” and “trials” refer to HIV prevention clinical trials in phase II or phase III, specifically microbicide and pre-exposure prophylaxis (PrEP) trials, involving female study participants.

APPENDIX

Table 2.2: Sample Not Involved in HIV Prevention Trials Perceptions Related to Contraceptive Issues (n = 47)

Statement	Strongly Disagree and Disagree % (n)	Agree and Strongly Agree % (n)
6. Non-barrier contraceptive methods should be required for participants in trials.	**57.6 (19)**	42.5 (14)
7. Non-barrier contraceptive methods should be offered to participants at all trials sites.	5.7 (2)	**94.3 (33)**
8. Participants should be denied participation in a trial if they refuse to use a non-barrier contraceptive method.	**85.3 (29)**	14.7 (5)
9. Emergency Contraception (EC) should be integrated into contraceptive services offered to study participants.	8.8 (3)	**91.2 (31)**
10. Emergency Contraception (EC) should be offered to study participants at the trial site (as opposed to through referrals).	12.2 (4)	**87.9 (29)**
11.All trial participants should be required to use a long-term method of contraception (Norplant or IUD)	**84.4 (27)**	15.6 (5)
12.All trial participants should be offered a long-term method of contraception (Norplant or IUD)	8.8 (3)	**91.1 (31)**
13. Providing on-site contraceptive services and counseling to trial participants is a viable way to improve preventive care practices.	8.8 (3)	**91.2 (31)**
14.All trial sites should be linked or co-located with a family planning service or clinic	24.3 (8)	**75.7 (25)**

Note: The terms “trial” and “trials” refer to HIV prevention clinical trials in phase II or phase III, specifically microbicide and pre-exposure prophylaxis (PrEP) trials, involving female study participants.

APPENDIX

Table 3: Total Sample Perceptions Related to Pregnancy Issues (n = 106)
(See Figure 5 for results displayed in a bar graph)

Statement	Strongly Disagree and Disagree % (n)	Agree and Strongly Agree % (n)	# of comments (n)
15. If a woman becomes pregnant during a trial, it should be the responsibility of the study to refer her to antenatal care services.	6.8 (5)	**93.2 (69)**	29 (74)
16. All trials should provide pregnancy options counseling (a term used to describe the different choices a woman has when she learns she is pregnant) to woman who becomes pregnant during the trial).	14.7 (11)	**85.3 (64)**	**27 (75)**
17. All trials should monitor pregnancy and birth outcomes of participants who become pregnant during the trial.	12.4 (9)	**87.7 (64)**	32 (73)
18. Pregnancy testing during trials should be conducted less frequently than once a month to help reduce detection of false or chemical pregnancies.	**58.8 (40)**	41.2 (28)	**33 (68)**
19. Pregnancy testing during trials should be done at least once a month to ensure that pregnancy is detected as soon as possible.	29.0 (20)	**71.0 (49)**	**26 (69)**
20. Preclinical and clinical safety and toxicity studies of microbicide candidate products should include studies of reproductive toxicity, teratogenicity, and carcinogenicity so that female participants who do become pregnant during the efficacy trials of these candidate products could possibly remain on product throughout trial.	11.3 (8)	**88.7 (63)**	29 (71)

Note: The terms “trial” and “trials” refer to HIV prevention clinical trials in phase II or phase III, specifically microbicide and pre-exposure prophylaxis (PrEP) trials, involving female study participants.

APPENDIX

Table 3.1: Sample Involved in HIV Prevention Trials Perceptions Related to Pregnancy Issues (n = 56)

Statement	Strongly Disagree and Disagree % (n)	Agree and Strongly Agree % (n)
15. If a woman becomes pregnant during a trial, it should be the responsibility of the study to refer her to antenatal care services.	5.0 (2)	**95.0 (38)**
16. All trials should provide pregnancy options counseling (a term used to describe the different choices a woman has when she learns she is pregnant) to woman who becomes pregnant during the trial).	17.5 (7)	**80.7 (33)**
17. All trials should monitor pregnancy and birth outcomes of participants who become pregnant during the trial.	7.5 (3)	**92.5 (37)**
18. Pregnancy testing during trials should be conducted less frequently than once a month to help reduce detection of false or chemical pregnancies.	**62.1 (23)**	37.8 (14)
19. Pregnancy testing during trials should be done at least once a month to ensure that pregnancy is detected as soon as possible.	38.9 (14)	**61.1 (22)**
20. Preclinical and clinical safety and toxicity studies of microbicide candidate products should include studies of reproductive toxicity, teratogenicity, and carcinogenicity so that female participants who do become pregnant during the efficacy trials of these candidate products could possibly remain on product throughout trial.	5.0 (2)	**95.0 (38)**

Note: The terms “trial” and “trials” refer to HIV prevention clinical trials in phase II or phase III, specifically microbicide and pre-exposure prophylaxis (PrEP) trials, involving female study participants.

APPENDIX

Table 3.2: Sample Not Involved in HIV Prevention Trials Perceptions Related to Pregnancy Issues (n = 47)

Statement	Strongly Disagree and Disagree % (n)	Agree and Strongly Agree % (n)
15. If a woman becomes pregnant during a trial, it should be the responsibility of the study to refer her to antenatal care services.	9.1 (3)	**90.9 (30)**
16. All trials should provide pregnancy options counseling (a term used to describe the different choices a woman has when she learns she is pregnant) to woman who becomes pregnant during the trial).	11.7 (4)	**88.2 (30)**
17. All trials should monitor pregnancy and birth outcomes of participants who become pregnant during the trial.	18.8 (6)	**81.3 (26)**
18. Pregnancy testing during trials should be conducted less frequently than once a month to help reduce detection of false or chemical pregnancies.	**53.4 (16)**	46.7 (14)
19. Pregnancy testing during trials should be done at least once a month to ensure that pregnancy is detected as soon as possible.	18.8 (6)	**81.3 (26)**
20. Preclinical and clinical safety and toxicity studies of microbicide candidate products should include studies of reproductive toxicity, teratogenicity, and carcinogenicity so that female participants who do become pregnant during the efficacy trials of these candidate products could possibly remain on product throughout trial.	20.0 (6)	**80.0 (24)**

Note: The terms “trial” and “trials” refer to HIV prevention clinical trials in phase II or phase III, specifically microbicide and pre-exposure prophylaxis (PrEP) trials, involving female study participants.

APPENDIX

Figure 1: Percent of sample involved in work on clinical HIV prevention trials (n=56) and percent of sample not involved in work on clinical HIV prevention trials (n=47) that agrees/strongly agrees with statement 8.

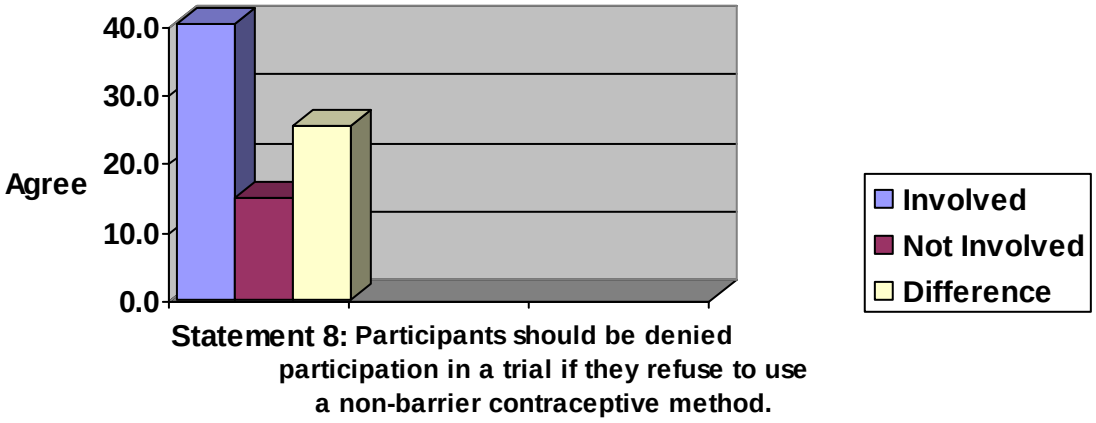
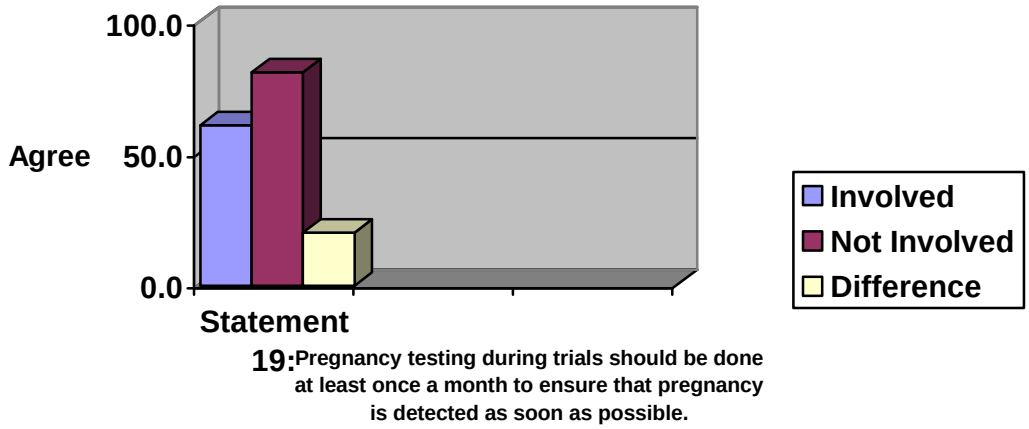


Figure 2: Percent of sample involved in work on clinical HIV prevention trials (n=56) and percent of sample not involved in work on clinical HIV prevention trials (n=47) that agrees/strongly agrees with statement 19.



APPENDIX

Figure 3: Percent of sample involved in work on clinical HIV prevention trials (n=56) and percent of sample not involved in work on clinical HIV prevention trials (n=47) that agrees/strongly agrees with statement 20.

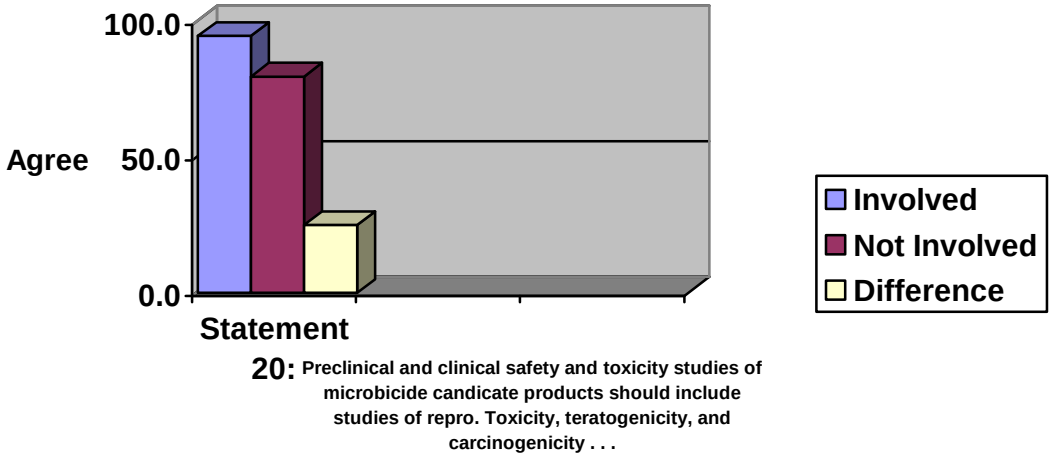
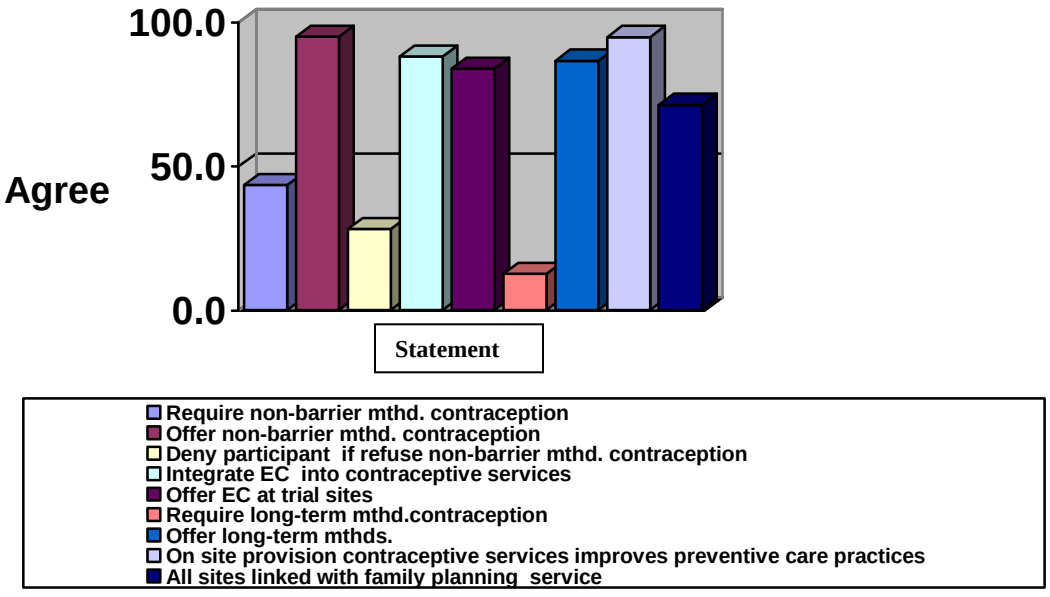
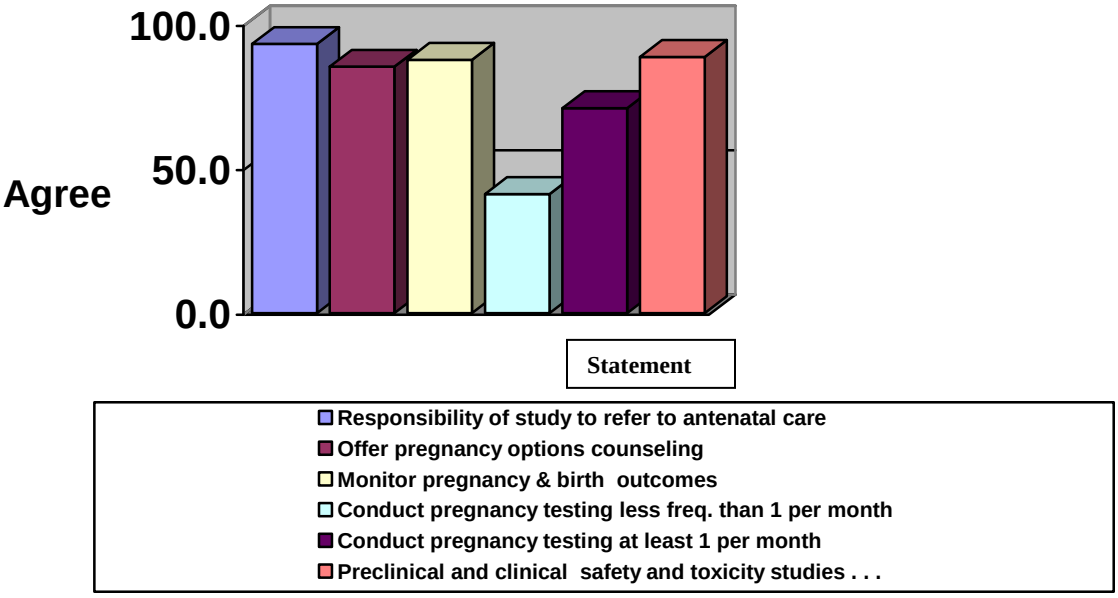


Figure 4: Percent of total sample (n=106) that agrees/strongly agrees with each statement related to contraceptive issues in clinical HIV prevention trials



APPENDIX

Figure 5: Percent of total sample (n=106) that agrees/strongly agrees with each statement related to pregnancy issues in clinical HIV prevention trials



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