MTN-041

Qualitative Assessment of Acceptability of Vaginal Ring (VR) and Oral Pre-exposure Prophylaxis (PrEP) Use during Pregnancy and Breastfeeding

Microbicide Trials Network

Funding Agencies:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
ARV	antiretroviral
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAB	community advisory board
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CRS	clinical research site
CWG	Community Working Group
DAIDS	Division of AIDS
DLV	Delavirdine
EC	Ethics Committee
EFV	Efavirenz
FBO	faith-based organization
FGD	focus group discussion
FTC	Emtricitabine
FTP	File Transfer Protocol
GCP	Good Clinical Practices
HCP	health care provider
HHS	Department of Human and Health Services (US)
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
IDI	in-depth interview
IND	investigational new drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IPV	intimate partner violence
IRB	Institutional Review Board
KI	key informant
LOC	Leadership and Operations Center
MSM	men who have sex with men
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
MO	Medical Officer
NIH	National Institutes of Health
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OHRP	Office for Human Research Protections

PBMC	peripheral blood mononuclear cell
PK	pharmacokinetics
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PTID	Participant Identification
QC	quality control
RSC	Regulatory Support Center
RTI	Research Triangle Institute
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSA	sub-Saharan Africa
SSP	study specific procedures
STD	sexually transmitted disease
STI	sexually transmitted infection
TBA	traditional birth attendant
TDF	Tenofovir Disoproxil Fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
VR	vaginal ring

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MTN-041

Qualitative Assessment of Acceptability of Vaginal Ring (VR) and Oral Pre-exposure Prophylaxis (PrEP) Use during Pregnancy and Breastfeeding

INVESTIGATOR SIGNATURE FORM
Version 1.0; October 31, 2017
A Study of the Microbicide Trials Network

Funded by:
Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases
US Eunice Kennedy Shriver National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health (NIH)

IND Sponsor:
A Non-IND Study (DAIDS Protocol ID: 38161)

I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); standards of the International Conference for Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to DAIDS, unless otherwise specified by DAIDS or the Microbicide Trials Network (MTN) Leadership and Operations Center (LOC). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. DAIDS will inform the investigator/institution as to when these documents no longer need to be retained.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record (print)

_____ _____
Signature of Investigator of Record Date

MTN-041

Qualitative Assessment of Acceptability of Vaginal Ring (VR) and Oral Pre-exposure Prophylaxis (PrEP) Use during Pregnancy and Breastfeeding

PROTOCOL SUMMARY

Short Title: Microbicide/PrEP Acceptability among Mothers and Male Partners in Africa (MAMMA)

Funders: Division of AIDS, NIAID, NIMH, NICHD, US NIH

Protocol Chair: Ariane van der Straten, PhD, MPH

Protocol Co-Chair: Petina Musara, BSW

Sample Size: Up to 240 men and women, including up to 40 key informants (KI)

Study Population:

- HIV-uninfected women aged 18-40 who are currently pregnant or breastfeeding, or who were pregnant or breastfeeding within the previous two years
- Men aged 18 or older whose partners are currently pregnant or breastfeeding, or whose partners were pregnant or breastfeeding within the previous two years
- Maternal and paternal grandmothers whose daughters or daughters-in-law are currently pregnant or breastfeeding, or were pregnant or breastfeeding within the previous two years
- KI in the community aged 18 or older, including health care providers (HCP) and traditional birth attendants (TBA)

Study Sites: MTN-041 site(s) selected by the MTN Executive Committee

Study Design: Exploratory acceptability study that will utilize focus group discussions (FGDs) and in-depth interviews (IDIs)

Study Duration: Approximately 3-6 months for recruitment and enrolment at each site

Primary Objectives:

- To explore attitudes about use of a vaginal ring (VR) during pregnancy and breastfeeding, including participants' willingness to use or recommend/support use of a VR during pregnancy and breastfeeding

- To explore attitudes about use of oral PrEP during pregnancy and breastfeeding, including participants' willingness to use or recommend/support use of oral PrEP during pregnancy and breastfeeding

Secondary Objectives:

- To explore potential preference for a VR or oral PrEP during pregnancy and breastfeeding
- To explore participants' attitudes about and perceptions of sexual activity during pregnancy and breastfeeding, including how a VR or oral PrEP might affect sexual activity and contraceptive use
- To explore participants' perceptions of HIV risk during pregnancy and breastfeeding
- To explore community beliefs and practices considered taboo or encouraged during pregnancy and breastfeeding that might affect VR and PrEP uptake and use during these periods, including use of oral medications and intravaginal products

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Qualitative Assessment of Acceptability of Vaginal Ring (VR) and Oral Pre-exposure Prophylaxis (PrEP) Use during Pregnancy and Breastfeeding
Protocol Number:	MTN-041
Date:	October 31, 2017

1.2 Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 Microbicides, Oral Pre-exposure Prophylaxis (PrEP) and Human Immunodeficiency Virus (HIV) Prevention

In 2012, 2.3 million people became newly infected with HIV and 1.6 million people lost their lives to acquired immunodeficiency syndrome (AIDS). Every 60 seconds, a young woman is infected with HIV.[1] According to the Joint United Nations Programme on Human Immunodeficiency Virus (HIV)/AIDS (UNAIDS) Global Report, the estimated number of individuals living with HIV is 35.3 million globally. Women and girls continue to be disproportionately affected by HIV in sub-Saharan Africa (SSA), where women account for approximately 60% of people living with HIV. Female controlled prevention options remain a global priority given the high rates of HIV infection among women. The ongoing development of safe and effective HIV prevention technologies that can be made easily accessible to developing countries remains a public health priority.

Between 1990 and 2004, HIV prevalence among pregnant women who attended public sector health care facilities in South Africa increased from 0.8% to 30.2%, staying at that level through 2010.[2] It was estimated that 70.4% of all maternal deaths in South Africa in 2011 were related to HIV infection, along with half of all deaths for children under five years old, prompting the scale-up of existing programs for prevention of mother-to-child transmission (PMTCT).

Pregnant and breastfeeding women in areas with high HIV incidence rates, particularly in SSA, are at high risk of acquiring HIV.[3] Biological factors during pregnancy and breastfeeding increase susceptibility to HIV infection; for example, elevated hormonal levels, untreated sexually transmitted infections (STIs), and changes in the vaginal microbiome associated with genital or cervical inflammation, as well as nutritional deficiency and lowered immunity. Also, social and behavioral factors during pregnancy and breastfeeding may increase exposure to HIV infection; for example, reduced condom use and increased intimate partner violence (IPV). Furthermore, pregnant and breastfeeding women who acquire HIV at this time have a greater risk of transmitting HIV to their infant than women who became infected with HIV before pregnancy because recent seroconversion leads to elevated viral loads and to reductions in the placenta's protective ability to block the virus from crossing from mother to baby.[4]

Unprotected heterosexual intercourse is currently the leading mode of HIV acquisition among women. Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition. However, condoms are widely regarded as inadequate prevention options for women because many women are unable to negotiate condom use with their partners. This is likely more difficult for women to do during pregnancy and breastfeeding, when contraception is not a motivating factor for condom use and male partners may be more resistant to use them during sex. Thus, developing HIV prevention options that women, particularly pregnant and breastfeeding women, can use remains a global concern.

In 2014, the World Health Organization (WHO) developed recommendations for offering oral pre-exposure prophylaxis (PrEP) containing the antiviral drug tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), to select key populations at high risk of HIV infection.[5,6] The WHO further expanded these recommendations in 2015 to include all persons at high risk of HIV infection, and then in 2016 stated that the benefits of PrEP for pregnant and breastfeeding women at risk of HIV infection outweighed any potential risks from side effects.[5,6] The expansion of the WHO recommendations' scope was supported by mounting evidence that oral PrEP regimens containing TDF, when followed consistently, were safe, cost-effective, and highly efficacious in reducing HIV infection risk regardless of age, gender, PrEP regimen, or

sexual exposure method.[5-7] However, gaps still exist in our understanding of how best to systematically implement oral PrEP with a number of populations, including the need for additional safety, acceptability and adherence data for HIV-uninfected pregnant and breastfeeding women.

Vaginal microbicides, which are self-initiated and controlled, offer women a critically needed biomedical prevention tool that will complement existing HIV prevention strategies as well as future products that are being developed. With successful proof-of-concept that antiretroviral (ARV)-based microbicides reduce the risk of HIV-1 acquisition, confirmatory work and further trials involving different ARV compounds, formulations, and dosing strategies are required to improve upon the level of product effectiveness and to provide a range of options that will meet the needs of all potential end-users.

For a microbicide to be effective, it is essential that it be used correctly and consistently, and that it be acceptable to the user. In addition, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. Higher adherence to a product can translate into higher effectiveness of the product. It is likely that products that can be applied less frequently or products that can remain *in situ* for an extended duration will be more acceptable and will achieve better adherence. Vaginal rings (VRs) that need to be replaced monthly may have benefits over dosage forms that need to be used more frequently.

Multiple clinical trials have evaluated the safety of dapivirine in VRs, gels and in an oral formulation. These clinical trials support the favorable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations. The results from two recently completed Phase 3 safety and efficacy trials of the dapivirine VR, MTN-020 (ASPIRE) and IPM 027 (the Ring Study), both of which found the VRs to be safe and effective in reducing HIV-1 infection in healthy female adults in SSA when used for one month and replaced monthly, would indicate the need to expand studies of the dapivirine VR to additional populations, including pregnant and breastfeeding women.

2.2 Description of Microbicides and Oral PrEP

2.2.1 Dapivirine VR

The International Partnership for Microbicides (IPM) has investigated a wide range of dosage forms for the development of topical microbicide products, including vaginal gels, rings, films, tablets and soft gel capsules. However, the dapivirine silicone elastomer VR has now been prioritized over all other dosage forms for the following reasons:

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month;
- Since the ring is able to deliver drug for at least 1 month, the burden of user-dependent adherence is lower than for once daily products;
- Product acceptability studies and the experience gained from marketed VR products have established a high level of acceptance and adherence from women using VR with similar physical characteristics;
- The overall cost for the VR is relatively low;
- Minimal storage space is required for the VR when compared with once daily products

Multiple clinical trials have evaluated the safety of dapivirine in VRs, gels and oral formulations. These clinical trials support the favorable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations. To date, 29 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted, with all but two completed:[8]

- Eight trials of dapivirine VRs (containing 25 mg and 200 mg loads) in which 298 participants were assigned to receive dapivirine VRs,
- Eight trials of dapivirine vaginal gel in which 491 participants were assigned to receive dapivirine vaginal gel,
- Eleven trials of oral dapivirine in which 211 participants were assigned to receive oral dapivirine.
- And, two trials of dapivirine vaginal film in which 71 participants were assigned to receive dapivirine vaginal film.

Additionally, two recently completed Phase 3 trials, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), evaluated long-term safety and efficacy of the 25 mg dapivirine VR (Ring-004), in which the VR was replaced with a new VR after approximately 28 days of use. A total of 4588 participants were enrolled between the two studies, with 2620 assigned to receive dapivirine VRs.[9-11] Across both trials, the dapivirine VR reduced HIV risk by 27.4%, with higher protection levels for those participants who were >21 years old and/or who used the VR consistently as indicated. The dapivirine VR had a low incidence of product-related AEs, with no clinically relevant differences between dapivirine and placebo VR groups. The incidence of serious AEs and Grade 3 and 4 AEs were also low and similar between the two groups. Permanent discontinuation of the dapivirine VR due to AEs occurred very rarely. Although exposure to dapivirine after HIV-1 infection was limited, a similar proportion of women in both groups had non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations identified soon after HIV-1 infection, and there was no clinically significant difference in the proportion of participants with mutations associated with resistance to efavirenz (EFV) and nevirapine (NVP). Although exposure to dapivirine during pregnancy was very limited, pregnancy rates were low and pregnancy outcomes were similar in both groups. Across all clinical trials with multiple ring configurations in healthy participants, the dapivirine VR was generally safe and well-tolerated.[8]

Acceptability of and Adherence to Dapivirine VR

Multiple clinical trials have evaluated the acceptability of the dapivirine VR among reproductive-aged women in Africa.[12-14] Overall, trial participants reported the VR was soft, flexible and comfortable, did not interfere with their daily activities, and that they were willing to use it if it was found to be effective for HIV prevention. Participants also found the VR easy to insert and remove, and appreciated the monthly regimen and its discreetness. Early concerns about safety and VR expulsions were typically overcome with actual ring use experience and staff and peer support. Women differed on whether and how VR use impacted their sexual experience, though most reported that their partner did not feel the ring during sex. Most women agreed that disclosure of VR use to partners was important to prevent relationship problems. The actual or perceived dynamics of participants' male partner relationship(s) were the most consistently described influence, both negative and positive, on participants' acceptability of the ring.

Multiple clinical trials have also evaluated adherence to the dapivirine VR among reproductive-aged women in Africa and the US.[9,11-14] Adherence was assessed either by self-report or by objective measures such as residual dapivirine concentrations in used rings or blood plasma dapivirine levels. Self-reported adherence to VR use was very high overall, with >80% of

participants across studies saying they used the ring every day. Residual VR and blood plasma drug levels supported these findings, although adherence was likely overestimated in the ASPIRE trial given that participants who used the VR for only a portion of the month would have been categorized as adherent as per the study definition of adherence. Subgroup analyses of residual ring data suggest that the majority of women inconsistently used the VR throughout their participation in ASPIRE.[11]

The most commonly stated activities that led to voluntary removal of the VR were cleaning, menses and sexual intercourse, while the most commonly stated activities that led to involuntary expulsions of the VR were urination/defecation and sexual activity. Reasons for removing the VR included: male partner's wishes, menses, and perceived side effects. In ASPIRE, drug detection appeared to increase after the first months of VR use and become stable after the first year, which may indicate that some time was needed for participants to become comfortable with the VR. Staff and peer support activities were seen as important platforms for motivating adherence, helping participants overcome concerns about VR use and trial participation, receiving feedback on their VR use experiences and fostering a sense of a shared goal. The actual or perceived dynamics of participants' male partner relationship(s) were the most consistently described influence, both negative and positive, on participants' use of the VR.

2.2.2 Truvada Oral Tablet

Truvada® was originally approved by the US Food and Drug Administration (FDA) in 2004 in combination with other ARV agents as a treatment of HIV-1 infection in adults and has become the most-prescribed ARV in the United States. Gilead Sciences, Inc. received US FDA approval in 2012 for once-daily oral Truvada® (FTC and TDF), in combination with safer sex practices, to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. Truvada® is the first agent to be approved for HIV prevention in uninfected adults, known as PrEP.[15] Truvada® for oral PrEP has also been approved for use by adults at high risk of sexually acquiring HIV-1 infection in a number of other countries, including two of the MTN-041 study countries, South Africa and Zimbabwe.[16]

Truvada® for oral PrEP has become an important part of large-scale HIV-prevention efforts for the following reasons[5-7]:

- Clinical trials have demonstrated that oral PrEP containing TDF reduces HIV infection risk in a wide variety of settings and populations;
- ARV drugs are becoming safer, more efficacious, and more affordable;
- New and improved HIV testing technologies offer greater opportunities to monitor and detect acute HIV infection, reducing the chances of promoting TDF-resistant HIV strains;
- The overall cost-effectiveness of targeted oral PrEP is relatively high; and
- Daily tablet regimens have high acceptability among most providers and target populations.

A review[17] of seven completed PrEP randomized clinical trials with a combined 18,747 female and male participants, including the iPrEX (Iniciativa Profilaxis Pre-Exposición), Partners PrEP, the Bangkok Tenofovir Study, FEM-PrEP, VOICE and CAPRISA 004 trials, evaluated safety, efficacy, adherence and potential barriers to 'real-world' uptake. Across all trials, reduction in HIV risk provided by oral TDF alone or in combination with FTC ranged from 0%–75%. TDF-based oral PrEP did not increase rates of serious (grade 3 or 4) adverse events (AEs) in any studies. In some studies the risk of nausea, vomiting, diarrhea, unexplained weight loss, fatigue, and

dizziness was higher than with placebo. Side effects were generally mild, infrequent (affecting 1%–10% of participants), and disappeared after 1 to 2 months of use. Drug resistance was rare among participants who were HIV-negative at enrollment but became infected during follow-up (0%–12% of incident cases); however, resistance was frequently observed in those who started PrEP while already infected (up to 100% of such cases). Additional analyses from the Partners PrEP data suggests the Truvada oral tablet would be safe to use in early pregnancy.[18]

Furthermore, in the Partners Demonstration Project, a prospective implementation study of 1013 newly-recruited, high-risk heterosexual HIV-1 serodiscordant couples in Kenya and Uganda, PrEP was offered to the HIV-uninfected partner as a 'bridge' until the HIV-infected partner initiated antiretroviral therapy (ART) and was on ART for at least 6 months, which is sufficient time for viral suppression.[11] The study was concluded in July 2016, achieving an estimated 95% reduction in HIV incidence compared to a counterfactual HIV incidence.

Acceptability of and Adherence to Truvada Oral Tablet

Multiple clinical trials have evaluated the acceptability of and adherence to the Truvada oral tablet among reproductive-aged women in Africa.[11,18-26] One study conducted with female sex workers in Kenya found the Truvada tablet a feasible and highly acceptable product regardless of dosing schedule (daily, twice weekly, or within two hours after sex); however, another study conducted with South African women found the pericoital dosing schedule to be a poor fit with their usual post-sex routines. The latter study, HPTN 067, found acceptability could be enhanced by interpersonal support, personal belief in PrEP's efficacy, cellphone and other reminders, and keeping pills at hand, and that a daily dosing regimen may lead to better habit formation and more forgiveness for missed doses.

Adherence was assessed by self-report, returned pill count, and/or blood plasma drug levels. Overall, Truvada tablet adherence tended to be high by self-report (>88% across studies) and returned pill counts (>75% across studies), but less consistently so by blood plasma drug levels (from <30% in VOICE to 86% in the Partners Demonstration Project). Most VOICE participants did not use the study products daily, a finding that is not consistent with pre-study assessments of the willingness of the target populations to use such products, adherence assessments based on clinic-based product counts and self-reporting, and the high rates of retention. Lower adherence in VOICE was associated with characteristics that predicted a higher risk of HIV acquisition. Results were consistent with those of the FEM-PrEP trial, in which daily Truvada use did not reduce HIV-1 acquisition among women and in which study drug adherence was also low. However, VOICE results markedly differed from those of Partners PrEP, which displayed a significant reduction in risk of HIV-1 acquisition. Of note was that VOICE participants who were most likely to adhere were similar in terms of age and marital status to women in the Partners PrEP trial. The VOICE trial highlights the need for biomarker measures of adherence that do not rely solely on self-reporting and that are not easily manipulated by participants, such as real-time biologic monitoring of drug levels.

Barriers and facilitators to adherence were assessed in the HPTN 067 and FEM-PrEP trials. Facilitators included: participant's support for the research, HIV risk reduction, personal experiences with persons living with HIV/AIDS, strategies and tools such as adherence counseling and reminder alerts, social and emotional support (e.g., from partners and clinic staff), material support (e.g., financial reimbursement and clinical care). Barriers included: concerns about side effects, community stigma and distrust, privacy concerns (e.g., disclosure to partner, being identified as an HIV positive person), negative clinic or research participation experiences, and Truvada tablet characteristics (e.g., odor, size). Lastly, data from Partners PrEP and other

Phase 3 PrEP trials like iPrEx and VOICE indicate that adherence at early time points predict adherence over the next one to two years, suggesting that adherence-focused interventions should occur as soon as possible after initiation of PrEP.

2.3 HIV Risk Perception and Motivation to Use HIV Prevention Products

One possible factor that may contribute to low uptake of HIV prevention products among women is varying perceptions of HIV risk over their lifetime. A woman's perception of HIV risk is influenced by her individual level behaviors, such as engagement in high-risk sex, as well as the social-cultural context in which she lives. This perception of risk has often been linked to willingness to participate in hypothetical HIV prevention trials[27-37] and occasionally to interest in and acceptance of an HIV prevention product.[38]

Despite these linkages, the question remains: how does one's perception of HIV risk contribute to product acceptance and product uptake? One might expect that a higher perception of risk would lead to higher product acceptability and uptake due to a greater desire for protection. However, a recent study in India casts doubt on this hypothesis, finding that increased HIV risk perception was negatively associated with consistent gel use, as women who perceive themselves at higher risk may be less able to adhere to product use for a host of contextual reasons.[39] Further, it is not well understood how individual women's risk perceptions and product use motivations might change during pregnancy and breastfeeding. By investigating how the socio-cultural environment influences perception of risk, product acceptability and ultimately product uptake among pregnant and breastfeeding women, this study hopes to contribute to a greater understanding of the relationship between these issues.

Other motivations for using an HIV prevention product during pregnancy and breastfeeding, such as community norms around taking medications, sexual activity and vaginal practices of pregnant and breastfeeding women, and their contribution to product acceptability will also be explored.

2.4 Role of Male Partners in HIV Prevention and Antenatal Care

Another possible factor that may contribute to low (or high) adherence is male partners' attitudes about research studies, HIV prevention strategies, HIV treatment and prevention medications, intravaginal products, and/or oral tablets. In many countries around the world, especially in SSA, men are conferred the power to make health-related decisions for the family, including sexual and reproductive health issues. In some countries, 75% of women report that their male partners make health decisions related to women's health such as HIV-related prevention and treatment programs, including HIV testing and counseling, uptake and adherence to ARV therapy and follow-up appointments.[40] Tackling traditional gender norms and gender inequality has been emphasized by UNAIDS as an important strategy to curb and reverse the HIV epidemic in that region. [41] Thus, men should be included in HIV prevention programs as their active participation is pivotal to the implementation and success of such programs.

When men actively participate in HIV prevention services like couples HIV testing and counseling, they and their partners experience multiple benefits. Studies suggest that people in couples who get tested together and mutually disclose their HIV status are more likely to adopt behaviors to protect their partner than those who do not get tested or who get tested alone. In a serodiscordant couple, the provision of ART to the positive partner can significantly reduce the risk of transmission to the negative partner and the provision of oral PrEP to the negative partner can help to prevent HIV acquisition. [40]

Research shows that active involvement of male partners plays a positive role in increasing the effectiveness of female-oriented programs for reproductive health and HIV prevention and treatment, including women's uptake of HIV testing, uptake of and adherence to ART treatment, and selection of infant feeding options. In studies involving pregnant women, participants were more likely to accept HIV testing when their male partners attended antenatal visits with them during pregnancy [42] Women also reported a higher uptake of PrEP,[43] better adherence to ART treatment,[44,45] and better adherence to the recommended infant feeding option when their male partners participated in PMTCT services.[43,46] Male partner engagement with PMTCT services was also positively associated with decreased infant HIV incidence and mortality and better HIV-free infant survival.[47-50]

A small number of studies explored possible adverse effects of male involvement in women's health and identified several potential drawbacks such as disruption of family relationships, physical violence and emotional abuse, and abandonment from partners and spouses.[51-54] In one study, participation in a PMTCT program in Malawi resulted in numerous divorces due to the program's request for partner disclosure.[55] In another study, women in a couples testing and counseling intervention group were significantly less likely to receive HIV testing and results than women in the control group with female individual counseling only.[56]

Despite those drawbacks, mounting evidence suggests that male involvement needs to be enhanced in HIV prevention and PMTCT programs. However, male partner participation levels are currently low in SSA. According to the WHO, the percentage of pregnant women in low- and middle-income countries receiving HIV testing increased from 21% in 2008 to 35% in 2010, with an increase from 45% to 61% in the highest burden areas of eastern and southern Africa, but the proportion of pregnant women who test with their partners is extremely low.[40] A survey of 388 men in Uganda also suggested that male participation in antenatal care was far from satisfactory, with only 5% of those surveyed ever accompanying their spouses to the antenatal clinic.[57] The lack of full male partner engagement represents one of the key obstacles to women's access to PMTCT services, and consequently may undermine the potential benefits of antenatal HIV prevention efforts.

Researchers have looked at factors affecting men's participation in their spouses' HIV antenatal care, and have identified barriers at multiple levels. Several review articles categorized these into societal/cultural, health system, information/knowledge, and individual-level barriers. The overriding societal/cultural barriers were the perceptions of antenatal care and pregnancy as purely a woman's affair. The gender norm that women are not allowed to lead men and the societal ridicule of men accompanying their wives to antenatal clinics were also important impeding factors.[58] At the health system level, long waits and male-unfriendly atmosphere at the clinic, health workers' hostile attitude, and distrust in confidentiality of the health system were reported as major barriers.[59] At the individual level, some sociodemographic characteristics contributed to low male engagement, including older age, lower education, and lower income and/or resources.[49] Another set of barriers were related to men's information/knowledge gap, including the misconception that their HIV status is the same as their wives, limited knowledge of PMTCT, being unaware of the importance of male involvement, and availability of male-friendly HIV testing and counseling services.[51,58] Other frequently reported barriers included work commitments, financial burdens, and weakening of relationship with spouses.[60-62]

Multiple facilitators to encourage male involvement in HIV prevention and PMTCT program were also identified and classified into similar groups at societal/cultural, health system and individual levels. Sending invitation letters to male partners to ask for their participation was identified as the first and foremost health system facilitator, followed by offering routine voluntary couples

counseling, providing services in non-working hours and at sites other than antenatal clinics, encouraging open discussion among couples about HIV testing and counseling, organizing community sensitization activities, and providing ARVs in health centers.[49,58] At the individual level, older age, higher level of education, previous experience of HIV testing, increased knowledge of HIV and perceived benefits of PMTCT were associated with better involvement in HIV-related antenatal care.[58,59] Other facilitators included monogamous marriage, stable relationship, open discussions of PMTCT among couples, and sero-concordant HIV status.[43,47,63]

In the context of research on HIV prevention and microbicides, a small subset of studies investigated male partner's role in women's participation into microbicide clinical trials and product use. Even though microbicides have been designed as female-initiated products that help to promote women's autonomy and independence, studies demonstrated that male partners' understanding, awareness and acceptance of research trials and microbicides exert important direct and indirect influence on women's participation in studies as well as their self-reported product adherence.[64-66] In a clinical trial of a diaphragm and lubricant gel for HIV prevention, 995 Zimbabwean women were asked about their male partners' influence on their study participation and product use. Only 45% of female participants reported that their partner ''strongly'' supported the use of the diaphragm and gel, and only 31% and 26% of them said their partners ''strongly likes'' the diaphragm or gel, respectively. Another study synthesized findings of six qualitative studies on microbicide use in South Africa, Kenya, and Tanzania. It was found that most men either opposed their partners' participation in studies and their partners' use of microbicides, or provided ony tacit permission to use microbicides, and only a minority provided active support, instrumental or emotional, to their partners for product use.[67] Secondary data (both qualitative and quantitative) from the ASPIRE, VOICE, CAPRISA 008, and other trials, as well as the above qualitative review, showed that for some women, microbicide use improved communication with partners, reinforcing product adherence.[68] However, it increased conflicts with partners and the risk of IPV for others.

Microbicides were designed to give women an HIV prevention tool they can use without a male partner's involvement, but research suggests that the approval or support of male partners is often desired, or even required, to enable women to use microbicides. By investigating the role that male partners can have in women's use of the VR and oral PrEP, this study hopes to contribute to a greater understanding of this important component of uptake and adherence, including possible ways to mitigate opposition and cultivate support among men and communities for HIV prevention research, HIV prevention products, and microbicide use.

2.5 Role of Key Community Members in HIV Prevention and Antental Care

As stated earlier, in SSA men have traditionally been conferred the power to make health-related decisions for the family, including sexual and reproductive health issues. However, women are discouraged from discussing sexual and reproductive issues with their male partners, and men rarely join their female partners in antenatal care visits. Given low levels of male partner involvement, it is practical for HIV prevention and antenatal care programs to only target women. Other community members, both male and female, have traditionally played key roles in women's decision-making related to HIV prevention and antenatal care services. These key community members include, but are not limited to: health care providers (HCP); traditional birth attendants (TBAs), midwives and other traditional care providers; religious leaders and other opinion leaders. These influential community members can be powerful supporters (or opponents) of HIV prevention and antenatal care practices through various means, including information dissemination, behavioral advocacy, providing or facilitating the provision of testing and treatment

services, monitoring medication adherence, and addressing HIV-related stigma and female empowerment.

2.5.1 Health care providers (HCP)

HCPs in Africa play a critical role in HIV prevention and antenatal care. HCPs offer education, provide HIV testing and counseling, conduct risk assessments, prescribe medications and monitor medication adherence. HCPs' perceptions and attitudes about what is and is not acceptable to do during pregnancy and breastfeeding can have significant impact on the implementation and effectiveness of HIV prevention and antenatal care service provision. Whether a woman seroconverts during pregnancy, becomes pregnant while HIV-positive, or wants to prevent either or both, HCPs will likely contribute to the success of her sexual and reproductive health goals.

In 2015, the WHO recommended that oral PrEP be provided to all persons at substantial risk of HIV infection, including women of childbearing age and pregnant women.[40] For oral PrEP (and topical microbicides if approved) to be effective, uptake and adherence are essential. HCP buy-in will therefore be critically important. In recent years, a growing number of studies focused on HCPs' awareness of and attitudes towards PrEP, and on their actual prescribing behaviors. These studies, conducted with HCPs across the world, suggested that overall, they were aware of PrEP but many lacked in-depth knowledge of PrEP. [69-73] While the majority of HCPs reported favorable attitudes towards the use of PrEP, only a small number of them actually prescribed it to their patients. In one study in Guatemala, 69% of providers were PrEP-aware, but only 9% of them had prescribed it.[71] In another study of HIV care providers in the US, only 25% reported having prescribed PrEP.[73] The populations to whom HCPs were most likely to prescribe PrEP were men who have sex with men (MSM) and HIV-negative partners in serodiscordant relationships.[74] HCPs voiced some concerns and cited many barriers to wider implementation of PrEP, including concerns about efficacy, side effects, development of resistance, cost, and an increase in high-risk behaviors.[71,75,76] HCPs expressed a need for more training and clinical support to implement PrEP.[76-78]

While HCPs' support for PrEP is crucial, active participation of pregnant and breastfeeding women will be equally indispensable to successful implementation of PrEP/microbicides for HIV prevention. One factor that could deter women from fully participating is their perception of HCPs' attitudes towards HIV/AIDs prevention and care. In SSA, as in many parts of the world, HIV stigma is deeply rooted and persistent. Unfortunately, HCPs are not immune from exposure to stigmatizing cultural norms or from exhibiting resultant discriminatory behaviors in their professional practice. HIV-related stigma and discrimination may manifest as refusal to provide care for patients, refusal to touch an HIV-infected patient, using harsh language and blaming patients for their HIV status.[79] In a survey of 254 randomly selected Nigerian HCPs, the overall attitude towards people with HIV was poor. 56% of them felt that people with HIV are responsible for their illness, and only 53% were willing to work with them.[80] Another study showed that more than half of Ethiopian HCPs in the study reported a fear of HIV transmission at work, lack of safety, and exercising extra precautions around people with HIV.[81] Similar unfavorable and negative attitudes towards people with HIV were identified in studies of Malaysian medical students.[82]

Provider stigma may have detrimental effects on the prevention and treatment of HIV. For people living with HIV, perceived stigma in the clinics may discourage disclosure of HIV status.[83] and deter them from accessing needed care and treatment.[84,85] HIV stigma has also been associated with poor treatment adherence and increase in risk behaviors.[85,86] In the context of HIV prevention for pregnant and breastfeeding women, this could lead to worsening outcomes for not just the women, but also their infants and their families.

For people who are HIV-uninfected but at high risk of exposure, such as women living with HIV-positive men or men with unknown status, perceived stigma may discourage their adoption of prevention behaviors and uptake of prevention products like oral PrEP and topical microbicides. Pregnant women are especially vulnerable to HIV-related stigma as they are often the first family member to receive HIV testing when they go to an antenatal care clinic, and thus may be blamed for bringing the virus to the family if they test positive for HIV.[6] Studies suggested that fears of HIV testing and consequent unwanted disclosure prevented some women from accessing antenatal care services altogether.[87,88]

In addition to pregnant women, HCP stigma also hindered their male partners' active engagement in antenatal care. Previous research has identified HCPs' negative attitudes and behaviors as one barrier for partner participation. In some studies, men described HCPs' attitudes as embarrassing, rude, and harsh,[89] HCPs' language to pregnant women and their partners as abusive,[60,89,90] and HCPs' contact with pregnant women's bodies as worrisome,[57] all of which contributed to their lack of participation.

2.5.2 Traditional birth attendants (TBA), midwives and other traditional care providers

HCPs are an important influence in women's sexual and reproductive health decision-making. Nevertheless, mainstream Western medical practice coexists with a number of equally influential indigenous health beliefs represented in the practices of a whole spectrum of traditional care providers, including TBAs, midwives, herbal and spiritual healers. The WHO defined traditional medicine as "diverse health practices, approaches, knowledge and benefits incorporating plant, animals and or mineral based medicines, spiritual therapies, manual techniques and exercise applied singularly or in combination to maintain wellbeing as well as to treat, diagnose or prevent illness."[91]

Traditional care providers' practice includes two major components: the physical and the spiritual. They may use plants, animal parts, and/or minerals in preparing medications for the body, and may also practice other therapies such as acupuncture, massages, incantations, sacrificial offerings and other rituals for both body and spirit.[92] Unlike most Western medicine, traditional medicine treats a patient as a whole person and addresses all physical, psychological, spiritual and social symptoms. Therefore, traditional medicine is both a reflection of and a contributor to the cultural and religious beliefs of local communities and tribes.[93] Being well-respected and highly consulted practitioners, traditional care providers play an indispensable role promoting well being as health, religious and spiritual guides, legal and political advisors, and marriage and family counsellors throughout Africa.[94]

Even though traditional medicine was banned in many African countries during the colonization of the continent, these practices persisted and survive to this day, and remain easily accessible and widely used by people. In SSA, the ratio of traditional care providers to the general population is approximately 1:500, compared to the 1: 40,000 ratio of biomedically trained HCPs to the general population.[95] In Uganda, there is one traditional care provider for every 200-400 people, in contrast to 1 biomedically trained HCP for every 20,000 people.[91] It is estimated that about 80% of the African population uses traditional medicine to meet their health needs, and in South Africa, 60-80% consult a traditional care provider before seeing a primary care doctor.[93]

In SSA, only 46% of women give birth in a health facility with a trained nurse-midwife or doctor, while 22% deliver at home with TBAs, 26% deliver at home with relatives, and 6% deliver at home with no attendant at all.[96] TBAs are normally elderly women with many years of experience in

tending to the needs of pregnant women prior to and during childbirth. Their major duties include teaching women to avoid certain behaviors during pregnancy, delivering the babies, ritually disposing of the placentas, and providing traditional medicines and massages after delivery. They also advise women on postpartum care, breastfeeding, marriage, contraception and fertility in general.[92] For compensation, many birth attendants do not charge for their service, usually accepting presents instead.

Due to their accessibility, acceptability and affordability, their familiarity with local culture, customs and traditions, and their status in many communities, public health experts have advised that TBAs and other traditional care providers be integrated in efforts to tackle the HIV/AIDS epidemic. Although there is still debate about the lack of scientific rigor of traditional medicine therapies and the potential harms it may do to people, experts generally agree that collaboration should be attempted for practical reasons to meet the demand for health services. For over 20 years, the WHO has advocated the inclusion of traditional care providers in national AIDS programs, and in recent years, some nongovernmental agencies have intensified efforts to promote their role in HIV prevention and care.[97]

There has been a lot of discussion on how best to incorporate TBAs and other traditional care providers in the fight against HIV/AIDS. First, because of their reputation and influence with women when it comes to fertility, STI and HIV related issues, they are in a great position to help disseminate knowledge and information about STI/HIV prevention and antenatal care to their clients.[98] Second, traditional care providers can be involved in traditional medicine organizations at international research conferences and workshops and encouraged to conduct research on specific traditional beliefs and practices.[93] Lastly, traditional care providers can collaborate with HCPs by cross referring patients to each other when treatment within their respective expertise is deemed appropriate. Studies show that traditional care providers have expressed their enthusiasm and willingness to collaborate with HCPs.[97]

Researchers have studied the collaboration between HCPs and traditional care providers since the 1990's, including projects assessing herbal remedies' effectiveness to treat AIDS and related diseases, and traditional care providers' perceptions towards STIs and HIV/AIDS. However, the majority of these projects were designed to train traditional care providers as educators and counsellors to disseminate HIV/AIDs information and prevention practices among their clients and peers. In 2000, UNAIDS conducted a review of 25 collaboration projects implemented in countries across Africa. The eight projects with the most evaluation data were selected to assess their effectiveness, efficiency, ethical soundness and sustainability based on UNAIDS Best Practice criteria. Overall, these projects reported a significant increase in knowledge among trained traditional care providers regarding HIV/AIDS symptoms, transmission, and prevention methods. Traditional care providers also reported retaining information after training, training fellow providers, counselling clients in HIV prevention and care, and developing their own HIV education materials to use in local communities.[97] In addition, they reported increasing their referrals to health centers and discussing condom use with clients as well as actively distributing condoms.[98] The review concluded that these projects generally met the criteria for ethical soundness but were extremely difficult to sustain over the long term. Efficiency was difficult to evaluate due to lack of measures and data in these projects.[97] Several projects working with TBAs also reported success in training them to perform rapid HIV testing and dispense NVP to mothers and babies in remote villages in Cameroon and Tanzania.[99,100]

2.5.3 Religious leaders and other opinion leaders

Besides HCPs and traditional care providers, religious leaders also play a key role in women's sexual and reproductive decision-making, being central and integrating figures in the social and cultural life of most local communities. In many African countries, there are more religious leaders and faith-based organization (FBO) workers than HCPs. Situated within local communities, they are in regular and close contact with the people, developing trusting relationships with community members of all age groups. In some traditional communities, religious leaders are highly respected and often more influential than local government officials, secular community leaders, and HCPs.[101] Churches have a long history of providing health care and education in African countries. In many instances, the church serves as a place of worship, a meeting place for social interaction and action, and a locus of community.[102] FBOs not only provide their followers with spiritual guidance, but also with a variety of health and social services, and therefore often are able to influence the attitudes and behaviors of local community members.

There has been abundant research on the connection between religion and health. Religion has been shown to influence a wide variety of health-related attitudes and behaviors, including HIV prevention, reproduction, contraceptive use, use of health services and others.[103] A considerable body of literature has looked at the relationship between religion and health, and results indicate that religious involvement has a beneficial effect on health behavior and outcomes.[104-106] Studies present consistent and convincing evidence that high levels of religious involvement are moderately associated with better general and mental health status.[105,107]

There have been frequent calls for churches in Africa to play a greater role in empowering local communities to fight against HIV/AIDS since the advent of the HIV/AIDS epidemic.[108] Religious leaders and FBOs can play a critical role in the prevention and control of HIV/AIDS given that churches have well-established community networks that can reach the most remote areas, and that their teachings of love, compassion and tolerance can motivate people to provide health care and other social services to the most vulnerable communities.[109] Working with families and other community organizations, churches are in an ideal position to understand local conditions and needs, facilitate the inclusion of people living with HIV/AIDS into the greater community, and help mitigate HIV/AIDS related stigma.[102]

Previous research reviewed the role of churches and FBOs in HIV/AIDS care and prevention, and revealed a complex and at times contradictory picture.[101,109] In many ways, the church perpetuates HIV/AIDS-related stigma due to its conservative views on sexual morality and gender roles.[108] The church frames HIV/AIDS in the language of sin and punishment, which can alienate affected church members and lead to self-stigmatisation, feelings of anger, and withdrawal from religious involvement.[110,111] The association of HIV/AIDs with sin and shame limits more open discussion of this topic and further reinforces existing stigma. In some instances, when church leaders made efforts to encourage open discussion about HIV/AIDS, they faced strong opposition from more senior pastors.[112]

While HIV-related stigma and discrimination may be spread by and may be widespread within FBOs, there is evidence that church groups are actively involved in the care and support of people living with HIV/AIDS. Their services include: provision of medical care (e.g., tuberculosis and STI treatment, and providing ARVs in some settings), home-based care, counselling and pastoral care, psychological care, food and material support for families and orphans, income generation activities and support groups.[109,113] The care and support provided by religious leaders and FBOs, even though limited and unbalanced across countries and areas, have greatly alleviated the suffering of many people living with HIV/AIDS, both physically, psychologically and spiritually.

In comparison to care and support activities, church leaders and FBOs have traditionally been less active in HIV prevention, primarily because the church's prevention messages often clash with mainstream HIV prevention approaches.[109] For example, churches often focus on promoting abstinence and fidelity as prevention strategies, while mainstream health, governmental and non-governmental organizations emphasize condom use, voluntary HIV testing and STI treatment. [108] Many religious leaders strongly oppose the use of condoms and consider it a tool for unfaithful wives, connecting condom use with immorality and suggesting that only nonbelievers are at risk of contracting HIV. This view can create a false sense of security among church members and lead to risky and unsafe sexual behaviors on their part.[101]

In summary, the response from religious leaders and FBOs to HIV prevention and care has been uneven. Prevention methods promoted by FBOs can prevent the spread of the HIV virus, as indicated by some studies showing the social and sexual control of church members through messages of fidelity and abstinence can lead to a reduction of high risk sexual behaviors, including reductions in sexual partners and in pre- and extra-marital sexual activities.[114,115] However, the effect is variable depending on the characteristics of different religious denominations.[108] In HIV care and support, FBOs' active involvement alleviated people's deep suffering and provided them much needed help and services. However, the debate between "realistic" versus "moralistic" approaches to HIV prevention is still alive and religious leaders often are deadlocked with mainstream stakeholders over condom use and mandatory HIV testing before marriage.[101]

Despite the limitations, church leaders and FBOs still play an indispensable role in HIV prevention and care. In more recent years, some churches explored alternative forms of social control for prevention and tried to open new supportive social spaces to challenge and mitigate stigmatizing ideas and practices.[108] For instance, in some settings, churches can create conditions to allow members to disclose their HIV-positive status to church leaders more easily.[111] In other settings, churches can encourage members to renegotiate understandings of HIV/AIDS in more positive and less morally charged ways to help initiate actions to tackle HIV/AIDS related issues and problems.[116]

Over the years, various groups and organizations have implemented HIV intervention programs in FBOs, and their effectiveness on improving HIV knowledge and preventative behaviors has been mixed. A study from Ghana explored the association between women's knowledge of HIV/AIDS and their religious affiliation and found that religious affiliation had a significant effect on knowledge of AIDS but was not associated with changes in protective behavior, specifically the use of condoms.[117] Smith found that popular religious teachings about HIV led to inconsistent protective sexual practices in youth because they perceived themselves at little or no risk.[118] Young female church members were found to be more likely to delay sexual initiation, but less likely to use condoms during sex.[119] However, other studies indicated that religion was an important predictor of risk behaviors, especially pre- and extra-marital sexual activities.[114,115,120] Later studies found that different Christian denominations had varying levels of influence on church members' sexual behaviors. Spirit-type churches were found more likely to influence members' alcohol consumption and extra-marital affairs than Mission churches in Zimbabwe.[121] In South Africa, only Pentecostal churches were found to significantly reduce members' pre- and extra-marital sexual activities.[120] In Malawi, Trinitapoli found that men in Pentecostal churches consistently reported lower levels of HIV risk behavior and perceived HIV risk. Specifically, when pastors delivered HIV prevention messages more frequently, monitored members' sexual behavior and encouraged condom use privately, church members reported greater adherence to abstain, be faithful and use condoms.[122]

2.6 Community Norms around Pregnancy and Breastfeeding

The previous section described the diversity of stakeholders and opinion shapers in SSA when it comes to women's use of HIV prevention and antenatal care services, including the important role of traditional care providers during pregnancy and childbirth. This section will describe in more detail some of the diverse cultural practices and beliefs regarding pregnancy and childbirth that have been shaped by this diverse pool of stakeholders. These beliefs and practices continue to influence women's sexual and reproductive health, and understanding how they may contribute or hinder the implementation of microbicides and oral PrEP for HIV prevention in pregnant and breastfeeding women will be key to reaching this vulnerable population.

In many countries, pregnant women often engage in indigenous healing and cleansing practices for the baby and themselves, including taking herbal remedies and ritual bathing, spreading smoke or spraying substances around the house.[123] The main reason for these practices is the need for protection of the mother and child, e.g., to strengthen the womb against sorcery, to prevent childhood illness, and to treat ailments that mainstream HCPs are unable to help. Although HCPs generally discourage traditional healing practices during pregnancy, both pregnant women and traditional care providers assert that these practices address women's needs that biomedical care does not.[123] In a survey of 218 women in South Africa, 87% of the participants said it was acceptable to go to a traditional healer or take herbal medicines and attend an antenatal care clinic at the same time during pregnancy.[124]

When pregnant women suffer from minor ailments, many go to a traditional care provider or self medicate with herbal remedies at home. One herbal remedy widely used by Zulu women in South Africa is called isihlambezo, a liquid mixture of various herbs. Traditional care providers promote its multiple benefits for women and infants during and after pregnancy. During pregnancy, it is thought to help women relieve edema and vaginal wetness, prevent backache and sexually transmitted diseases (STDs), and clean their womb/stomach. For the fetus, isihlambezo supposedly reduces placenta size, stimulates fetal growth, and prevents miscarriage and premature delivery. During labor, it is thought to facilitate a quick and painless delivery, reduce vernix and liquor at delivery, and speed up post-partum healing.[124] Both Xhosa- and Afrikaans-speaking women in South Africa reported using herbal remedies, such as Buchu, while Afrikaans-speaking women also apply liquid dish soap to the abdomen to loosen the baby before birth. In Uganda, women eat emumbwa, a clay bar made with soil and herbs, to make the pelvic bone more flexible and ensure an easier and less painful delivery. Despite experts' warning that the clay could be harmful to mothers and their unborn babies, emumbwa remains popular as women attest to its effects on relieving morning sickness and other pregnancy-related symptoms.[125]

In addition to herbal remedies, people follow other cusdoms during pregnancy and childbirth. For instance, in Zimbabwe, pregnant women are supposed to return to their parental home when they are 6-7 months pregnant to perform certain rituals that help cervical dilation.[126] In Uganda, there is a childbirth ritual named Okufugika that involves burying the placenta under a banana tree in a banana plantation to make the child a clever person. The placenta is seen as a "second child", and if it is not buried properly, it is believed the human child becomes unintelligent.[125]

Pregnancy is considered a delicate time in a woman's life, and in SSA it is believed to be the time that is most vulnerable to witchcraft. Witchcraft, or *umego*, may harm the mother and unborn baby as well as cause preterm birth and miscarriage. If a pregnant woman walks over some *muti* (generally referring to botanical medicines) planted by others, she will go into labour immediately.[127] In Malawi, pregnant women and their families should avoid quarrelling with

people for fear of giving witches opportunities for bewitchment.[128] In Zimbabwe, early pregancy should be kept a secret to avoid bewitchment, and women should also avoid blood screening as the blood drawn could be used to bewitch them. Pregnant women go to traditional or faith healers as they are believed to possess special powers that can protect them from harm.[126]

During pregnancy, women are also expected to forego certain practices. In some African cultures, it is forbidden to insert anything into the vagina, especially during pregnancy.[127] In Malawi, pregnant women are not supposed to take any "bitter" medicine, traditional or biomedical, such as "capsules" or anti-malarials.[128] A pregnant woman should also avoid coming into contact with impurity, which is believed to be responsible for preterm birth and miscarriage. A woman is seen as "impure" when she is sexually active, has vaginal bleeding, or has experienced a recent death in the household.[128] Taboos on food preparation for pregnant women are also related to impurity, for example, that they should avoid foods cooked or prepared by an unknown person because it could have been prepared by an impure woman.[128]

After childbirth, feeding the baby becomes an important consideration, and infant feeding practices in SSA are heavily influenced by a multitude of social, cultural and policy factors. Studies show a high degree of variability in feeding practices within and between countries. A multicenter study on the knowledge, attitudes and practices of pregnant women in SSA found that long breastfeeding periods were common practice, with only 2.4% of respondents weaning their children before 6 months.[129] Though exclusive breastfeeding is traditionally preferred in some countries, and 46.5% of the HIV-infected women surveyed preferred exclusive breastfeeding, mixed feeding is extremely common. The same study found over 87% of respondents introduced other fluids and foods in the first 6 months. Mixed feeding was more common in rural areas, while acceptance of exclusive formula feeding was significantly higher in urban areas.[129]

Research has identified several factors that have an impact on infant feeding practices in SSA. For women living in households with extended family, female relatives (mother, mother-in-law, aunts) can have a strong influence on their infant feeding practices.[129] In some countries, recommendations from government and health organizations also play a big role in feeding practices. Prior to 2011, the South African government promoted formula feeding by making it freely available at public health facilities. Due to the WHO guidelines on HIV and infant feeding, the state stopped providing free formula and has since supported exclusive breastfeeding.[130] Marketing strategies by private enterprise have also affected infant feeding practices. Advertisements for formula promote the idea that breast milk substitutes (BMS) are superior to breast milk, and have appealed to the notion that BMS will address infant hunger, especially if the mother is malnourished. Furthermore, formula manufacturers often give financial incentives to HCPs to help promote their product.[131] Another key factor influencing infant feeding practices in SSA is the high HIV infection rate. It is recommended that HIV-infected mothers do not breastfeed if they are able to access formula for the entire infancy period, given the risk of HIV transmission to the baby via breast milk. In countries where resources and access to health care are limited, it is risky to advise HIV-positive women to use BMS because mixed feeding poses an even higher risk of HIV transmission to infants than breastfeeding alone. Due to this concern, the WHO now advises women to breastfeed regardless of HIV status in countries where infection and malnutrition are the leading causes for infant death.[131] But, given the same information, the government of Lesotho now supports mixed feeding as an option for HIV positive mothers.[132]

As with pregnancy, nursing mothers are advised to forego certain practices after childbirth, particularly sexual activities.[133] Sexual abstinence after childbirth is a widespread practice in SSA and has been cited in multiple studies.[63,133,134] There are different reasons why lactating women and their male partners should refrain from having sex. One belief is that sexual activitiy is seen

as “heating” the woman’s body, which will change the quality of her breast milk and make it less nutritious.[135] Another belief is that mother's milk turns “bad” and can transmit sickness, evil and even cause death to the baby when the mother transgresses by having extra-marital sexual intercourse.[133] Semen is also believed to make breast milk impure.[136] Whether it is the mother or father who breaks the abstinence requirement, there are negative impacts on the baby’s health, including diarrhea and even death. While this taboo exists for both men and women, men are only expected to abstain for the first 3-4 months while women are required to abstain for the duration of the breastfeeding period.[135] One study reports that these different expectations for men and women has led to increased rates of HIV and STIs during the breastfeeding period, as men seek out other sexual partners due to the longer period of abstinence for their female partners.[137]

Another post-partum taboo for women in SSA is that they must stop breastfeeding if they become pregnant again during lactation. This is based on the notion that pregnancy increases body temperature and turns the mother’s milk back into colostrum. Since the milk now belongs to the baby in the uterus, if an infant drinks the milk, s/he will have diarrhea and vomitting. In Tanzania, a woman who becomes pregnant while breastfeeding also faces moral judgment by others as it is a clear sign that she has not adhered to the abstinence requirement. Furthermore, her baby will be deprived of breast milk since she now must stop breastfeeding, exposing the mother to social stigma and doubts about her role as a good mother.[135,136]

2.6.1 Role of maternal and paternal grandmothers

In many societies around the world, older women are considered carriers of traditional knowledge and thus play a significant role in both their family and their community. Maternal and paternal grandmothers in particular have a powerful and multifaceted role in the extended family unit, influencing everything from maternal and child health to family and marital relations, and even agricultural practices.[138] Research conducted on the relation between child nutrition and household dynamics across the world reveals two common themes. First, grandmothers play a central role as advisors to younger women on nutrition and health issues and as caregivers of both younger women and children. Second, the social networks of grandmothers exert collective influence on maternal and child health practices, especially on pregnancy, infant feeding and caring for childhood illnesses.[139]

Grandmothers are an important source of support for new mothers, and research shows they provide ongoing advice to women during pregnancy and after delivery. Their knowledge and personal experience with pregnancy and childbirth can influence their daughters’ and daughters-in-law’s decisions regarding pregnancy and child rearing, including whether they follow traditional pregnancy practices, initiate and continue breastfeeding, and access health care services for their children and themselves. In one study, women in Senegal reported that their grandmothers gave them various types of advice during pregnancy. For example, that they should wear talismans and drink herbal teas to protect them and the fetus from spiritual forces, that they should avoid certain foods that could harm the mother or the fetus, and eat a bit less to avoid having a large baby and a difficult delivery.[140] Grandmothers in general value breastfeeding and give precise advice regarding breastfeeding initiation and duration, such as waiting to initiate breastfeeding until the second or third day after delivery.[141] When maternal and child health is concerned, grandmothers were always consulted, not only by women but also by their husbands and other family members. During childhood illnesses, grandmothers play a leading role in diagnosing the illness, giving home remedy treatments, and advising on the need to take the sick child to traditional care providers or mainstream HCPs.[140]

In SSA, a growing number of studies have evaluated the role of grandmothers in breastfeeding practices. The WHO and other health organizations recommend exclusive breastfeeding for the first six months of an infant's life due to its enormous benefits in reducing childhood mortality and morbidity, but the rates of exclusive breastfeeding remain low in Africa, with the lowest rates among low- and middle-income countries (25%) found in the West and Central Africa region.[142] Breastfeeding practices are influenced by multiple interwoven factors, including economic, political, cultural psychosocial and health factors.[143] Research on the role of grandmothers indicates that various characteristics of grandmothers are associated with women's breastfeeding practices, including their education, their knowledge and attitudes towards breastfeeding, their prior personal breastfeeding experience, and whether they live with the infant's family.

Negin and colleagues conducted a systematic review of 13 studies on this topic. Eight studies examined the effects of attitudes or experiences of grandmothers on breastfeeding, and five of those studies found exclusive breastfeeding was significantly and positively impacted when grandmothers had breastfed or were positively inclined towards breastfeeding. Three of the thirteen studies reported negative impacts of grandmothers on breastfeeding, including one study that found if a paternal grandmother had a negative attitude towards breastfeeding or advised giving the infant water or tea, the mother was significantly less likely to initiate breastfeeding right after birth and more likely to abandon exclusive breastfeeding by the end of the first month. Another study found that if the grandmother was the primary caretaker of the infant, the mother was more likely to practice nonexclusive breastfeeding. [144] Grandmothers who did not practice exclusive breastfeeding were also more likely to exert pressure on younger mothers to discontinue exclusive breastfeeding, especially with the co-occurrence of lactation problems or health problems.[143]

Based on the research reviewed, it is evident that the role of maternal and paternal grandmothers on breastfeeding practices can be both supportive and inhibitory. On one hand, grandmothers across SSA generally prefer breastfeeding over BMS like formula, and tend to encourage their daughters to breastfeed for a longer period of time. On the other hand, they are considered obstacles in the promotion of exclusive breastfeeding since they tend to advise their daughters to breastfeed according to custom, introducing other liquids and foods within six months of childbirth. In the context of PMTCT, the traditional knowledge of grandmothers clashes with both the exclusive breastfeeding and exclusive formula feeding recommendations of the WHO and other health organizations. Thus, grandmothers often demonstrate a negative attitude toward this advice for HIV-infected mothers.[141,145]

Although grandmothers may become barriers to promoting safe and healthy feeding practices due to their powerful decision-making influence in maternal and child health issues, their influence can also become an asset if included in maternal and child health education interventions. In the past, most health education programs have focused on the mother-child dyad and few have addressed the role of grandmothers.[138] Recently there has been more of an effort to actively involve grandmothers in health interventions. For example, in Senegal, grandmothers were trained to promote good nutritional practices related to pregnancy and infant feeding. Evaluation of the intervention showed that there was significant increase in grandmothers' knowledge about nutrition and infant feeding and that they were more likely to advise pregnant women to follow these practices. Rates of exclusive breastfeeding also increased to above 90%.[140] This finding provided evidence that grandmothers are open to change, able to learn new knowledge, and use it to positively influence women's childrearing practices.

2.7 Rationale for Study Design

MTN-041 is an exploratory study primarily designed to identify individual, interpersonal, social and cultural factors that may affect potential uptake of two safe and effective HIV prevention products, the monthly dapivirine VR and daily oral PrEP, in a vulnerable yet seldom-studied population, pregnant and breastfeeding women. MTN-041 will utilize FGDs and IDIs to elicit community and health professional perceptions about vaginal practices, sexual activity, use of medicines, and HIV risk during pregnancy or breastfeeding, including how these perceptions may affect pregnant and breastfeeding women's acceptability of using intravaginal products and oral medications like the dapivirine VR and Truvada oral tablet.

There are relatively few published studies investigating use of HIV prevention methods by pregnant or breastfeeding women outside a PMTCT context. Although studies show that male partners play an important role in women's adherence to microbicides[68], more research is needed to understand how this might manifest in the context of pregnant and breastfeeding women's uptake of the dapivirine VR or of oral PrEP. Lastly, without buy-in from stakeholders and key leaders in their communities, it will be next to impossible to expand access to HIV-prevention methods for this vulnerable population. Therefore, perceptions relevant to the study objectives will also be elicited from male community members, grandmothers, and KIs, including HCPs and TBAs.

This study will also examine the role of the contextual environment on acceptability of intravaginal and oral products, and on prevention method preferences. Despite clinicians' best efforts to support adherence and/or discourage behaviors that may contribute to dilution of efficacy, the socio-cultural context,[146] including the clinical care context, organization of the participant's social environment (i.e., living arrangements, importance and role of partners, family members, and the larger social network), and individual beliefs and attitudes about HIV risk, may influence these behaviors. MTN-041 will explore the potential impact of this social context on pregnant and breastfeeding women's opinions about and willingness to use intravaginal products and oral medications like the dapivirine VR and Truvada oral tablet.

3 OBJECTIVES

3.1 Primary Objectives

- To explore attitudes about use of a vaginal ring (VR) during pregnancy and breastfeeding, including participants' willingness to use or recommend/support use of a VR during pregnancy and breastfeeding

- To explore attitudes about use of oral PrEP during pregnancy and breastfeeding, including participants' willingness to use or recommend/support use of oral PrEP during pregnancy and breastfeeding

3.2 Secondary Objectives

- To explore potential preference for a VR or oral PrEP during pregnancy and breastfeeding

- To explore participants' attitudes about and perceptions of sexual activity during pregnancy and breastfeeding, including how a VR or oral PrEP might affect sexual activity and contraceptive use

- To explore participants' perceptions of HIV risk during pregnancy and breastfeeding

- To explore community beliefs and practices considered taboo or encouraged during pregnancy and breastfeeding that might affect VR and PrEP uptake and use during these periods, including use of oral medications and intravaginal products

4 STUDY DESIGN

4.1 Identification of Study Design

The MTN-041 trial is a multi-site exploratory study using FGDs and IDIs to identify individual, interpersonal, social and cultural factors that may affect potential uptake of two safe and effective HIV prevention products, the monthly dapivirine VR and daily oral PrEP, by pregnant and breastfeeding women in Africa.

4.2 Description of Study Population

The MTN-041 study population will consist of HIV-uninfected women 18-40 years old who are currently or were recently (within two years) pregnant or breastfeeding, men aged 18 years or older whose partners are currently or were recently (within two years) pregnant or breastfeeding, grandmothers whose daughters or daughters-in-law are currently or were recently (within two years) pregnant or breastfeeding, and KIs who meet eligibility criteria as described in Sections 5.3 and 5.4.

4.3 Time to Complete Accrual

Approximately 3-6 months for recruitment and enrolment at each site. See Section 10.4 for additional details.

4.4 Expected Duration of Participation

The total duration of study participation for each participant is not anticipated to exceed 6 hours, including administrative and data collection procedures. However, the duration of participation is dependent upon the scheduling of IDIs or FGDs. Each IDI is not anticipated to exceed 2 hours and each FGD is expected to take up to 4 hours. Multiple visits may be conducted to complete all required procedures, if necessary.

4.5 Sites

MTN-041 participants will be recruited from clinical research sites (CRS) selected by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population

Up to 60 men and women will be selected at each site for participation in this study, for a maximum total of 240 study participants. This includes up to 50 FGD participants (currently or recently pregnant or breastfeeding women, male partners of women who are currently or were recently pregnant or breastfeeding, and grandmothers with currently or recently pregnant or breastfeeding daughters/daughters-in-law) and up to 10 KIs selected at each site, for a maximum total of 200 FGD participants and 40 KIs enrolled across all sites. Inclusion and Exclusion Criteria, Sections 5.3 and 5.4, respectively, are used to ensure the appropriate selection of study participants for MTN-041.

5.2 Recruitment

Participants will be recruited from selected study sites in Africa. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review. Community education strategies, including group sessions, may be employed as part of participant/partner outreach. Currently or recently pregnant or breastfeeding women's HIV status will be verified via health record review prior to enrolment for those potential participants who allow it (or by self-report if health record[s] not available); see Section 13.5 for additional details.

At each site, and in consultation with the Research Triangle Institute (RTI) team, community advisory boards (CABs) and project staff will be responsible for identifying the KIs to be interviewed. Target KIs include: HCPs, TBAs, providers of family planning, antenatal, and traditional health services to women; providers of other social services to women; and community leaders.

5.3 Inclusion Criteria

Potential participants must meet all of the following criteria to be eligible for inclusion in the study:

1. Able and willing to provide written informed consent in one of the study languages.

2. Able and willing to complete the required study procedures.

For currently or recently pregnant or breastfeeding women:

3. Between the ages of 18 to 40 years old (inclusive) at Enrolment, verified per site standard operating procedures (SOPs).

4. Currently or recently (within two years) pregnant or breastfeeding (by self-report).

For male partners:

5. Aged 18 years or older at Enrolment, verified per site SOPs.

6. Identifies as a primary sexual partner of a woman who is currently or was recently (within two years) pregnant or breastfeeding.

For grandmothers:

7. Aged 18 years or older at Enrolment, verified per site SOPs.

8. Identifies as the maternal or paternal grandmother of a daughter or daughter-in-law who is currently or was recently (within two years) pregnant or breastfeeding.

Note: The term "daughter-in-law" includes women who are/were not married to their male partner during or after pregnancy.

For service provider KIs:

9. Aged 18 years or older at Enrolment, verified per site SOPs.

10. Currently working as a clinician (e.g., obstetrician, nurse, pharmacist, etc.), traditional care provider (e.g., TBA, healer, midwife, etc.), social service provider (e.g., social worker, family planning counselor, etc.) or community health worker in one of the study countries, verified per site SOPs.

11. Experienced in providing services to pregnant and/or breastfeeding women.

For community leader KIs:

12. Aged 18 years or older at Enrolment, verified per site SOPs.

13. Currently acting in a community leadership role (e.g., local chief, religious leader, etc.).

5.4 Exclusion Criteria

Potential participants who meet the following criteria will be excluded from the study:

1. Has any condition that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

2. For currently or recently pregnant or breastfeeding women: known HIV-positive status, verified per recent health record (e.g., health passport, ante-natal book, HIV test card, or similar document) or by self-report if health record(s) not available.

6 STUDY PRODUCT

MTN-041 will not involve the administration of any study product.

7 STUDY PROCEDURES

7.1 Focus Group Discussions

Up to 200 men and women will be enrolled into MTN-041 for FGD participation (see Section 10.3.1 for sample composition details). Enrolled participants will be assigned into groups based on gender (male or female), role (grandmothers) and/or other characteristics (e.g., age, education, microbicide/PrEP exposure). Sites may assign participants into groups based on these characteristics after consultation with the MTN-041 Management Team if it is deemed that this categorization is both feasible and informative at the site(s). Final group designation at each site will be dependent on adequate sample size and representativeness of the recruitment pool.

Enrolled participants will be asked to complete a single FGD (with other participants in the same group assignment). Sites may ask enrolled participants to complete a single IDI instead of an FGD after consultation with the MTN-041 Protocol Team. The decision to conduct an IDI instead of an FGD will be dependent on adequate sample size and scheduling feasibility. The IDIs will also focus on individual and community perceptions of the topics listed above. Prior to completing the FGD (or IDI), enrolled participants will receive an introduction to the VR and oral PrEP using standardized materials.

Note: Specific information regarding group designation and assignment of enrolled participants to an IDI instead of an FGD will be specified in the MTN-041 SSP Manual, available at http://www.mtnstopshiv.org/studies.

7.1.1 Screening and Enrollment (Focus Group Discussions) – Administrative, Behavioral and Regulatory Procedures

Table 1: Screening and Enrollment Procedures – Focus Group Discussions

Screening and Enrollment – Focus Group Discussions	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent for screening and enrollment • Assign a unique Participant Identification (PTID) Number • Collect locator information • Provide reimbursement for study visit
Behavioral	• Provide introduction to VR and PrEP via standardized materials • Administer demographic and behavioral questionnaire(s) • Conduct Focus Group Discussion (FGD) or in-depth interview (IDI)

Multiple visits may be conducted to complete all required procedures, if necessary.

7.2 Key Informant Interviews

Up to 40 KIs will be enrolled into MTN-041 (see Section 10.3.2 for sample composition details). A single IDI will be conducted with each enrolled participant. Prior to completing the IDI, enrolled participants will receive an introduction to the VR and oral PrEP using standardized materials.

7.2.1 Screening and Enrollment (Key Informant Interviews) – Administrative, Behavioral and Regulatory Procedures

Table 2: Screening and Enrollment Procedures – Key Informant Interviews

Screening and Enrollment – Key Informant Interviews	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent for screening and enrollment • Assign a unique PTID Number • Collect locator information • Provide reimbursement for study visit
Behavioral	• Provide introduction to VR and PrEP via standardized materials • Administer demographic and behavioral questionnaire(s) • Conduct in-depth interview (IDI)

Multiple visits may be conducted to complete all required procedures, if necessary.

7.3 Behavioral Evaluations

The study will address questions related to the primary and secondary objectives of intravaginal product and oral medication acceptability facilitators and challenges experienced by pregnant and breastfeeding women, from the perspective of community members, including KIs such as HCPs and TBAs. The study will also explore community members' preferences related to HIV prevention methods for pregnant and breastfeeding women, and acceptable approaches to educate and market HIV prevention methods such as VRs and oral PrEP in this population. These questions will be assessed via behavioral questionnaires and either FGDs or IDIs conducted by trained interviewers/facilitators.

Additional questions and probes will be designed to delve further into the social and cultural norms that may play a role more broadly in product use acceptability and preferences for pregnant and breastfeeding women.

7.3.1 Behavioral Questionnaires

Demographic and behavioral questionnaires will be used to inform different dimensions of data collected during the FGDs and IDIs.

7.3.2 In-Depth Interviews (IDIs) and Focus Group Discussions (FGDs)

Both FGDs and IDIs will include, but not be limited to, topics such as:

- Perceptions of acceptable and/or typical vaginal and sexual practices during pregnancy and breastfeeding, including contraceptive use (when relevant)
- Perceived safety and acceptability of taking medications, oral or otherwise, during pregnancy and breastfeeding, for both the mother and the unborn fetus or breastfeeding infant

- Perceived norms related to women's autonomy and agency during pregnancy and breastfeeding, including the extent to which pregnancy may be medicalized in the community
- Perceived role of male partners in women's decision-making during pregnancy and breastfeeding, including how to engage them in efforts to scale up product roll-out and uptake
- Community beliefs and practices considered taboo or encouraged about pregnancy, childbirth and breastfeeding
- KI beliefs about pregnancy, childbirth and breastfeeding, including specific practices they encourage or discourage
- Attitudes and understanding of VR and oral PrEP efficacy and the concept of partial efficacy
- Socio-cultural context of risk behaviors (including sexual activity) and risk perceptions over time (before, during and after pregnancy), including concerns for the unborn fetus and/or breastfeeding infant
- Main challenge(s) perceived with VR and oral PrEP use during pregnancy and breastfeeding, including product uptake, storage, feasibility of continued product use, drug delivery modality and product attributes
- Main factor(s) perceived to facilitate VR and oral PrEP use during pregnancy and breastfeeding, including product uptake, storage, feasibility of continued product use, drug delivery modality and product attributes
- Other factors (e.g., situational, relationship, trial-specific, social/cultural/economic, sex related, contraceptive methods or other medications, etc.) perceived to influence VR and oral PrEP use patterns during pregnancy and breastfeeding
- Suggestions for recruiting and advertising research study participation to pregnant and breastfeeding women

FGD and IDI guides will be developed by qualified social scientists and administered by qualified interviewers in one of the study languages. Guides will contain questions and suggested probes relating to the main topics of interest. Interviews and discussion sessions will be audio-recorded.

Various tools may be used to facilitate interviews and discussion of sensitive topics with both FGD and IDI participants. These may include, but not be limited to, product facsimiles, video, pictures or show-cards listing topics and themes previously elicited in other studies.

8 ASSESSMENT OF SAFETY

MTN-041 does not involve a study product nor involve clinical, laboratory or other procedures associated with significant risk to participants. Therefore, the only anticipated risks as a result of study participation are social harms and embarrassment when discussing sensitive issues; see Sections 8.2 and 13.4.1 for additional details.

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants, and for alerting the protocol team if unexpected safety events occur. Study sites will have written procedures for ensuring prompt reporting to the IRB/EC of any unanticipated problem involving risks to subjects or others. No safety events will be captured in the study database. Untoward

clinical or medical occurrences reported by study participants to have been experienced during study participation will be managed appropriately and recorded in participant file notes.

There will be no expedited AE reporting in this study since there are no study products for which to report AEs.

8.2 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms – non-medical adverse consequences – may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be related to study participation will be reported to the DAIDS Medical Officer (MO), Protocol Chairs, and responsible site ECs/IRBs according to their individual requirements beginning at the time of enrollment (i.e., after a participant signs the informed consent and eligibility is confirmed) until study participation is complete. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-041 SSP Manual. While maintaining participant confidentiality, study sites may engage their CABs in exploring the social context surrounding instances of social harm. Additionally, a Standard Operating Procedure (SOP) for emergency procedures will be developed for the MTN-041 site staff to be used in situations of social harm and when situations that require immediate attention are identified, including domestic violence and suicidal ideation or behavior. The SOP will provide clear guidelines for site staff to refer participants in these situations to the relevant institution/body and to provide feedback to the protocol team.

9 CLINICAL MANAGEMENT

There are no additional clinical management considerations for participants enrolled in this study. Participants who express concerns with social, psychological or clinical issues will be referred for appropriate care to services available at the CRS, or at nearby partnering facilities.

9.1 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, including the Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may do so if the accrual target has not yet been met.

10 ANALYTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

MTN-041 is an exploratory study that will utilize FGDs and IDIs to identify individual, interpersonal, social and cultural factors that may affect potential uptake of two safe and effective HIV prevention products, the monthly dapivirine VR and daily oral PrEP, by pregnant and breastfeeding women in Africa.

The main goal of the study is to elicit community perceptions about the use of intravaginal products and oral medications during pregnancy and breastfeeding, including men's, women's, grandmothers', and KI's willingness to use or recommend/support use of a VR or oral PrEP during pregnancy and breastfeeding.

Secondary objectives of the study include the exploration of:

- Potential preference for a VR or oral PrEP during pregnancy and breastfeeding
- Participants' attitudes about and perceptions of sexual activity during pregnancy and breastfeeding, including how a VR or oral PrEP might affect sexual activity and contraceptive use
- Participants' perceptions of HIV risk during pregnancy and breastfeeding
- Community beliefs and practices considered taboo or encouraged during pregnancy and breastfeeding that might affect VR and oral PrEP uptake and use during these periods, including use of oral medications and intravaginal products

10.2 Study Endpoints

MTN-041 will explore individual and community perceptions of vaginal ring and/or oral PrEP use by pregnant and breastfeeding women. A single FGD with community members in the same group assignment (or a single IDI if an FGD is not feasible) will be conducted. In particular, the FGDs (or IDIs) will focus on:

- Perceptions of taboos and acceptable and/or typical practices during pregnancy, childbirth and breastfeeding
- Perceptions of HIV risk during pregnancy and breastfeeding
- Perceived role of male partners during pregnancy and breastfeeding
- Main challenge(s) perceived with VR and oral PrEP use during pregnancy and breastfeeding
- Main factor(s) perceived to facilitate VR and oral PrEP use during pregnancy and breastfeeding
- Willingness to join a VR and/or oral PrEP study during pregnancy and breastfeeding

MTN-041 will also explore KI perceptions of vaginal ring and/or oral PrEP use by pregnant and breastfeeding women. A single IDI will be conducted focusing on the topics listed above, as well as how others in their professional and social networks and communities would view the VR and/or oral PrEP use by pregnant and breastfeeding women.

10.3 Sample Size and Composition

10.3.1 Focus Group Discussions

A sample size of up to 200 male and female community members is targeted for FGD participation in this study. Two items were factored into the FGD sample size: the number of sites and the desired number of FGDs per site. First, it was important to have sites from each of the four (4) countries where the VR will be studied in pregnant and breastfeeding women represented in order to have a representative country sample. Second, a maximum of six FGDs (with approximately 6-10 participants per FGD) per site would be necessary in order to have up to two FGDs with currently or recently pregnant or breastfeeding women, up to two FGDs with male partners, and up to two FGDs with grandmothers. Thus, a sample size of up to 200 participants would be necessary for the FGDs.

Based upon participants' gender (male or female), role (mothers or grandmothers) and/or other characteristics (e.g., age, education, microbicide/PrEP exposure), community members will be categorized into groups. Final group categories at each site will depend on adequate sample size and representativeness of the enrolled participants, but may resemble the following:

- Currently or recently pregnant or breastfeeding women under 25 years of age
- Currently or recently pregnant or breastfeeding women 25 years of age and older
- Male partners of currently or recently pregnant or breastfeeding women under 25 years of age
- Male partners of currently or recently pregnant or breastfeeding women 25 years of age and older
- Grandmothers whose daughters or daughters-in-law are currently or recently pregnant or breastfeeding women

While the number of participants in each group at a given site is relatively small, we anticipate they will still be sufficient to reach theoretical saturation.[147] Furthermore, it is anticipated that participants will be representative of the overall pregnancy and breastfeeding trials by enrolling participants from each of the participating trial countries.

10.3.2 Key Informant Interviews

A sample size of up to 40 KIs is targeted for participation in this study. As with the FGDs, two items were factored into the KI sample size: the number of sites and the desired number of IDIs per site. First, four (4) sites are taking part in MTN-041. Second, up to ten (10) KIs per site would be necessary in order to achieve a representative spectrum of KIs at each site. Thus, a sample size of up to 40 KIs would be necessary for the KI interviews.

10.4 Participant Selection

MTN-041 FGD participants will be selected from a variety of sources across sites, including STD clinics, family planning clinics, and post-natal clinics, as well as community-based locations. In addition, participants may be referred to the study from other local research projects and other health and social service providers serving the target study population.

MTN-041 KI participants will be purposively selected by site CABs and project staff from health and social service providers working in health care facilities (e.g., public or private clinics and

hospitals) and community-based practices (e.g., home-based care, government or non-profit offices), as well as from influential community members (e.g., religious leaders, village elders, local celebrities). Sites will make efforts to ensure that a range of KI (e.g., HCPs, TBAs, traditional care providers, social service providers, community leaders, etc.) are adequately represented when selecting participants for the KI IDIs.

10.5 Data and Study Monitoring Procedures

Demographic and behavioral questionnaire data will be captured by case report form (CRF) and entered in an electronic database (e.g., Redcap). Qualitative data will be audio-recorded, processed (i.e., translated and transcribed in English), and coded for thematic analyses using Dedoose or a similar qualitative software. RTI International will function as the overall data coordinating center for quantitative and qualitative data and will lead all analyses.

No Study Monitoring Committee (SMC) review will be performed for MTN-041 given the short study timeline and the nature of the study. Protocol team members from MTN, including RTI International and FHI 360, will provide oversight of study operations and ensure the study is implemented in accordance with MTN standards, as defined in the MTN Manual of Operating Procedures.

10.6 Data Analysis

10.6.1 Quantitative Analysis

Demographic and behavioral questionnaire data will be captured by CRF and entered in an electronic database (e.g., Redcap). The following descriptive statistics will be used to assess the characteristics of MTN-041 participants: the number and percent in each category for categorical variables (e.g., gender, marital status, employment, pregnancy/breastfeeding status), and the mean or median and range for continuous variables (e.g., age, education, number of children, time since last pregnancy/breastfeeding).

10.6.2 Qualitative Analysis

Data Sources

The qualitative data from MTN-041 will include three main data sources:

- Original handwritten notes of FGDs and IDIs
- Audio-recorded FGDs and IDIs
- Transcripts of FGDs and IDIs

Qualitative Analysis Overview

The following section provides a brief overview of the analysis process; however, a more detailed description of the qualitative analysis will be presented in the study analysis plan.

Qualitative analyses from the MTN-041 study will use a variety of techniques to provide an in-depth characterization of the contextual factors that affected participants' perceptions of product acceptability and preference. The primary source of qualitative data used in the MTN-041 analysis will consist of raw textual data. Qualitative data will be audio-recorded, processed, and coded for qualitative analyses using Dedoose or a similar qualitative software. Data coding will be used as

a primary analytical approach for data reduction, that is, to summarize, condense, and extract meaning from the data.[148,149] MTN-041 transcripts will be coded first through descriptive coding for key themes and topics, using a preliminary codebook (see Section 10.6.3).[150] Additional codes will be identified through an iterative process of reading the textual data to identify emergent themes, and the codebook will be modified accordingly. In addition to descriptive codes, pattern codes and analytical memos, which achieve a greater level of abstraction, will be used to start linking themes and topics together in order to explore the relationship between socio-contextual factors, community norms, and product acceptability/preference.[149] Whenever possible, we will also compare study sites and explore differences or similarities related to product acceptability facilitators and challenges due to different socioeconomic, cultural and geographical contexts. The analysis will be done by the investigative team, working interactively through emails, and regular phone or face-to-face meetings. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data.[151]

10.6.3 Codebook Development and Coding Process[152]

Coding is an essential process for data reduction necessary for the management and interpretation of large amounts of qualitative data. Staff at RTI International will develop a codebook and study procedures for coding and analysis of all of the qualitative data. Each code will be operationally-defined and refined in an iterative way, as needed. Transcripts will be coded using a qualitative software package such as Dedoose.

During the study development stage, a set of preliminary codes will be developed based on the research questions of this study. The analysis coding structure will be hierarchical, and will reflect the topics/themes covered in the interview guides. After the first 2-3 interviews are completed, each member (analyst) of the coding group will apply this initial set of thematic codes to a common transcript, discuss their coding experiences (via email, a meeting, or conference call), and agree on expanding and modifying code names and definitions when necessary. The coding team will generate substantive and conceptual categories through an iterative process of reading the data, and generating codes based on the data and on key themes or topics identified *a priori*, applying the codes to the data, and refining these as coding progresses. Thus, codes will be centered on the main topics of interest (e.g., acceptability of VR and oral PrEP use during pregnancy and breastfeeding) and the hypothesized contextual spheres of influence. However, by nature, the qualitative research process is iterative, and the Dedoose software allows for the generation of new codes for emergent themes that were not identified *a priori* by the research team. The software also allows for coders to insert descriptive comments and memos to themselves and others as they are working, and to code for concepts not spelled out in verbatim text, such as “contradiction” when a participant contradicts herself, or “patriarchy” when a participant explains that she had to ask her husband for permission to come to the study visit.

Once finalized, the codebook will be used for coding of all of the transcripts. Comprehensive listings of all coded quotations for every code (as well as “families” of related codes) will be generated in Dedoose. The coding team will consider the coded dataset in its entirety, and “stratify” the coded quotations by the site, reported opinions of acceptability facilitators/challenges, reported opinions of product preference, and group assignment (e.g., male vs. female, HCP vs. TBA) when applicable. Depending on findings from the analysis of these data clusters, the team may conduct additional grouping and stratifications of the data.

The coding process will involve a core group of at least 2-3 analysts who will frequently communicate (via email, phone or in person meetings) and discuss their use of the codebook and

application of the codes during the coding process. A pre-selected proportion of inter-rater reliability tests using Dedoose or other coding software functions will be assessed with all coders. Following this process, the coding team will discuss (in person or via teleconference) the coding discrepancies, which will ultimately be resolved through consensus. Sufficient inter-rater reliability is defined as above .65 pooled kappa. Regular discussions among the coding team will ensure that coding remains standardized and reliable.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by RTI International in conjunction with the protocol team and will be manually double-entered in an electronic database. Quality control (QC) reports and queries will be routinely generated and distributed by RTI International to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents.

FGD and IDI guides will be developed by RTI International in conjunction with the protocol team and will be submitted to IRBs/ECs. Interview and group discussion files generated in the field will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using a qualitative software package. RTI International will act as a hub, and manage all data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. Transcripts will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf).

For MTN-041, source documentation may include recruitment logs, enrollment records, visit checklists, CRFs, interview data, participant file notes, and electronic audio files. Essential documentation for the study also includes all versions of the protocol, informed consent forms, operating procedures and key communication with the protocol team. In accordance with U.S regulations, each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study.

All sites will retain and store study records in accordance with DAIDS policy on Storage and Retention of Clinical Research Records (https://www.niaid.nih.gov/sites/default/files/Record_Retention_policyVersion2%20Final.pdf). Study records must be maintained on site for the entire period of study implementation. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS. Per DAIDS policy, clinical research records are the property of the awardee institution. Investigators and others retaining records covered under this policy will seek guidance from their

institution on whether or not the records are subject to any limitations on their disposal. Records relating to research and IRB/EC records will be retained for at least three years after completion of the research, as required by US Department of Health and Human Services (HHS) regulations 45 CFR 46.115(b).

11.3 Quality Control and Quality Assurance

At the field level, designated staff will check the quality of the transcripts and translations to ensure that they reflect the content of the interview, and then send each transcript to RTI International for additional QC. CRFs will be reviewed at the site and transmitted to RTI International where they will be reviewed and queried. All queries will be resolved through a standardized QC reporting mechanism.

All study sites will conduct QC and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported CRS (https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf).

12 CLINICAL SITE MONITORING

FHI 360 staff or designee will review study records during the course of the study, however no formal clinical monitoring will be conducted. FHI 360 staff or designee will do the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Assess implementation and documentation of internal site quality management procedures

The IoR/designee will allow inspection of study facilities and documentation (e.g., informed consent forms, clinic records, other source documents, CRFs), as well as observation of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the US OHRP, NIH, NIAID and/or contractors of the NIH, and other local, US or international regulatory authorities, and representatives of the MTN, as needed. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Boards/Ethics Committees

Site investigators will make every effort to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB/EC approval. The IoR will permit audits by the NIH, local

authorities, site IRBs/ECs, the MTN, OHRP, other local, US, or international regulatory authorities, or any of their appointed agents.

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent form, and study-related documents as required, are reviewed by an IRB/EC responsible for oversight of research conducted at the study site. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Each IoR/designee will make progress reports to the IRBs/ECs within three months after study termination or completion, unless specified otherwise by their IRBs/ECs. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. More real-time or frequent reporting of one or more of these or other items may need to be furnished if so specified by their IRBs/ECs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office (DAIDS PRO) in accordance with the most current DAIDS policies at the time of registration.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/ EC and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *will not* be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *will not* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

13.3 Study Coordination

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair and DAIDS MO. Study implementation will be guided by a common SSP manual that provides further instructions and operational guidance on conducting study procedures and associated data processing. Standardized study-specific training will be provided to all sites by FHI 360, RTI International, and other designated members of the Protocol Team.

13.4 Risk Benefit Statement

13.4.1 Risks

It is not expected that this trial will expose human subjects to unreasonable risk. Participation in research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing study-relevant behaviors, including vaginal and sexual practices, HIV prevention methods and microbicide use.

Psychological Harms

MTN-041 will ask questions that may cause individuals discomfort given their personal nature. Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics. This could result in undesired changes in thought and emotion.

While the risk of psychological harm is anticipated to be minimal, and study staff will inform participants that they can choose not to answer questions at any time, study staff will collect information on participants who report a change in mood as a result of study participation. In addition, study staff will ensure that participants have access to proper clinical resources to address psychological harms.

All FGD participants will be asked and strongly encouraged to respect each other's confidentiality, but participants who take part in the FGDs may still disclose what other participants said during the group discussion. Furthermore, all FGD participants will be asked to use pseudonyms for themselves and for anyone they may talk about during the course of the FGD.

Social Harms

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-positive or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Data on the occurrence of potential social harms will be collected from all participants. These data will be captured via CRF and analyzed on an ongoing basis. The protocol team will monitor, evaluate and adjust operations to reduce the potential for such occurrences.

13.4.2 Benefits

There are no direct benefits to participating in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader implementation of the dapivirine VR and oral PrEP. Participants may also appreciate the opportunity to contribute to the field of HIV prevention research.

Lastly, the information that participants provide may help health professionals develop better ways to improve communication and understanding between researchers and participants in HIV prevention studies.

13.5 Informed Consent Process

Each study participant will provide written informed consent prior to completing any study procedures. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

In addition to informed consent forms, the Protocol Team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, which will be detailed in the MTN-041 SSP manual. Furthermore, all potential participants from the 18-40 year old female FGD group will be asked to disclose their HIV status, if they know it, during pre-screening activities to ascertain presumptive eligibility to enroll in MTN-041. All potential participants will also be asked to bring health record(s), if available, to the Enrolment visit. Participants who bring their health record(s) to the Enrolment visit and give permission will have their HIV status verified prior to enrolling in MTN-041. Study staff will explain that their health record(s) will not be linked to information that could be used to identify them in any way. Only those women who agree to have their health record(s) reviewed during enrolment will have those records reviewed. Failure to bring health record(s) for review during enrolment will not be grounds for exclusion from the study. Only those women who provide access to their health records, or who self-report HIV-negative or HIV-unknown status if those records are not available, will be considered for further screening.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process will specifically address the following topics of importance to this study:

- The purpose of the study
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- There is no direct benefit to taking part in this study
- The right to withdraw from the study at any time

13.6 Participant Confidentiality

All study procedures will be conducted in a location agreed upon by the participant, and every effort will be made to protect participant privacy and confidentiality. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All study data collection and administrative forms will be identified solely by PTID number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms, will be stored securely. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PTID numbers to identifying information will be stored in a locked file in an area with limited access. All digital audio files will be stored on password-protected computers. Audio files will be translated and transcribed in English and securely stored. Please see MTN-041 SSP Manual for guidance. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US OHRP, NIH and/or contractors of the NIH, and other local, US or international regulatory authorities
- Study staff
- Site IRBs/ ECs

13.7 Special Populations

13.7.1 Pregnant Women

Pregnancy is not exclusionary. Due to the nonclinical nature of this study, no pregnancy-related risks are anticipated in MTN-041.

13.7.2 Children

MTN-041 will enroll male and female participants who are age 18 years or older at the time of enrolment for this study, as verified per site SOPs, as well as KIs including HCPs and community leaders, thus children will not be considered eligible for this trial.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms.

13.9 Study Discontinuation

This study may be discontinued at any time by NIH, the MTN, the US OHRP, other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies will govern publication of the results of this study.

15 APPENDICES

APPENDIX I: SCREENING AND ENROLLMENT SAMPLE INFORMED CONSENT FORM – FOCUS GROUP DISCUSSIONS

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-041

Qualitative Assessment of Acceptability of Vaginal Ring (VR) and Oral Pre-exposure Prophylaxis (PrEP) Use during Pregnancy and Breastfeeding

Version 1.0

FOCUS GROUP DISCUSSIONS

October 31, 2017

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Microbicide/PrEP Acceptability among Mothers and Male Partners in Africa (MAMMA)

INFORMED CONSENT

You are being asked to take part in this research study because you are an adult [***HIV-uninfected woman aged 18-40 years old / male partner of a woman / mother or mother-in-law of a woman***] who is pregnant or breastfeeding, or who was pregnant or breastfeeding in the last two years. Up to 240 men and women will participate in this study at multiple research sites in Africa. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Before you decide if you want to participate in the MTN-041 study, we want you to learn more about it. This consent form gives you information about this study. Study staff will talk with you and answer any questions you may have. Once you understand the study and its requirements, you can decide if you want to take part in it. If you decide to participate in this study, you will sign your name or make your mark on this form. A copy of this document will be offered to you.

[***For currently or recently pregnant or breastfeeding women:*** With your permission, study staff may request records from non-study medical providers to confirm your eligibility to join the study. By signing this form, you are giving the MTN-041 study team permission to have access to these records.] Your eligibility to participate in this study will then be assessed, and once confirmed, you will be considered enrolled in the study.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see “Your Rights as a Research Participant/Volunteer” section for more information).

WHAT IS THE PURPOSE OF THIS STUDY?
You are being asked today to take part in MTN-041. The main goal of this study is to better understand what may affect the use of two safe and effective HIV prevention methods, a vaginal ring (VR) and an oral tablet, by pregnant and breastfeeding women in Africa. To do this, study staff will ask your personal views, and what you think about [***you / women***] using vaginal products and oral medications during pregnancy and breastfeeding.

Most MTN-041 participants will be asked to participate in a focus group discussion (FGD) with other participants, but some may instead be asked to participate in an in-depth interview (IDI). Study staff will tell you if you are going to take part in an FGD or IDI.

STUDY PRODUCTS
No study products (investigational drugs or other products) will be tested in this research study.

STUDY PROCEDURES
The MTN-041 study consists of one study visit, which starts today after you sign this informed consent form. Additional visit(s) may be conducted to complete all required procedures, if necessary. Visits will take place here at this study clinic or at a place agreed upon by you and the study staff, which may be your home or another convenient location ***[SITE TO INCLUDE ALTERNATE LOCATION]*.**

The procedures done at this visit will take about ***[SITE TO INSERT TIME]****.*

- Study staff will ask you where you live and other questions about you, and your understanding of the study requirements.
- You will complete one or more written questionnaires where you will be asked some general questions, such as your age, education, living situation, relationship status, and health.
- You may be asked to participate in a FGD. If you're asked to join a FGD:
    - The FGD will take approximately ***[SITE TO INSERT TIME]***. Study facilitators will lead the discussion, fully explain the process, and answer any questions you have.
    - The facilitator(s) will talk with you about the two safe and effective HIV prevention methods of interest.
        - Daily oral tablet called Truvada, which is approved for pre-exposure prophylaxis (PrEP) to prevent HIV infection in multiple countries.
        - Monthly VR containing dapivirine, which is being considered for approval to prevent HIV infection in multiple countries.
    - In a small group setting with other study participants, the facilitator(s) will encourage discussion of various topics related to the use of vaginal products and oral medications by pregnant and breastfeeding women. The facilitator(s) will also encourage discussion about common beliefs and practices related to pregnancy, childbirth and breastfeeding, and about

possible educational and marketing approaches to promote use of vaginal and oral HIV prevention methods during pregnancy and breastfeeding.
    - The facilitator(s) will audio-record the FGD to make sure we record your words exactly how you said them.
    - A study staff member will take notes during the discussion as a backup to the audio-recording.
- If you are asked to have an IDI instead of an FGD:
    - You will have an IDI in the presence of one or two MTN-041 research staff members. The IDI will take approximately ***[SITE TO INSERT TIME]***.
    - The interviewer(s) will talk with you about the two safe and effective HIV prevention methods of interest.
    - The interviewer(s) will talk with you about various topics similar to those discussed during the FGD.
    - The interviewer(s) will then ask more questions, may take notes, and will audio-record your conversation.
- Study staff will also:
    - Tell you about other available health and social services, if needed.
    - Schedule your next visit, if necessary.
    - Reimburse you for your visit(s).

RISKS AND/OR DISCOMFORTS

During the interview (FGD or IDI), you may be asked some questions or have some conversations that cause you to feel embarrassed or uncomfortable. Trained study interviewers/facilitators will help you deal with any feelings or questions you have. You can choose not to answer questions or leave the room during the interview at any time.

Another possible risk of this study is loss of confidentiality of the information you give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, interviews will take place in private, and the information recorded during your interview will be strictly protected. You will be asked to use fake names for yourself and anyone you talk about to protect your identities. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. This means that no one other than the MTN-041 interview team will be able to link your responses to you personally. The audio recordings and any information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-041 study team for the purposes of this research.

If you participate in an FGD, other participants will hear what you say. Although we will not reveal your full name to other participants, it is possible that others may know you from previous interactions. We will also ask every participant not to tell anyone outside of the group what any person said during the FGD. While it is not likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private.

It is possible that others may learn of your participation here and treat you unfairly or discriminate against you because of it. For example, you could have problems getting or

keeping a job, or being accepted by your family or community. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS
There are no direct benefits to participating in this study. However, you and others may benefit in the future from information learned in this study. Participants in this study may also appreciate the opportunity to contribute to HIV prevention research efforts, including future research of HIV prevention products for pregnant and breastfeeding women. Information participants provide may help researchers improve counseling materials about product use and sexual behavior. Lastly, findings from this study may help health professionals improve communication and understanding between researchers and participants in HIV prevention studies.

Medical care for HIV infection and other health conditions will not be part of this study. This study cannot provide you with general medical care, but study staff will refer you to other available sources of care, if needed.

NEW INFORMATION
You will be told of any new information learned during this study that might affect your willingness to stay in the study. You will also be told when study results may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT
You may be removed from the study early without your permission if:

- The study is cancelled by the US NIH, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB) or Ethics Committee (EC). An IRB is a committee that watches over the safety and rights of research participants.
- You are unwilling or unable to comply with required study procedures, including study visit attendance.
- Other reasons that may prevent you from completing the study successfully.

COSTS TO YOU
There is no cost to you for study related visits.

REIMBURSEMENT
[*SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT*]: You will receive ***[SITE TO INSERT AMOUNT $XX]*** for your time, effort, and travel to and from the clinic at each scheduled visit.

CONFIDENTIALITY
Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- RTI International
- Site IRBs/ECs
- FHI 360
- Representatives of the US Federal Government, including the US OHRP, NIH and/or contractors of NIH, and other local, US or international regulatory authorities
- Study monitors
- Study staff

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY

[SITE TO SPECIFY INSTITUTIONAL POLICY]: It is unlikely that you will be injured as a result of study participation. If you are injured, the ***[INSTITUTION]*** will give you immediate necessary treatment for your injuries. You ***[WILL/WILL NOT]*** have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. NIH does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. If you want the results of the study after the study is over, let the study staff members know.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact ***[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]*** at ***[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]***.

If you have questions about your rights as a research participant, you should contact:***[INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]*** at ***[INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER]***.

SIGNATURES- VOLUNTARY CONSENT

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC]:

If you have read this consent form (or had it read and explained to you) and if you understand the information and voluntarily agree to take part in the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

APPENDIX II: SCREENING AND ENROLLMENT SAMPLE INFORMED CONSENT FORM – KEY INFORMANT INTERVIEWS

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-041

Qualitative Assessment of Acceptability of Vaginal Ring (VR) and Oral Pre-exposure Prophylaxis (PrEP) Use during Pregnancy and Breastfeeding

Version 1.0

KEY INFORMANT INTERVIEWS

October 31, 2017

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Microbicide/PrEP Acceptability among Mothers and Male Partners in Africa (MAMMA)

INFORMED CONSENT
You are being asked to take part in this research study because you are an adult from the community who has been identified as a key informant (KI) for this study. Up to 240 men and women will participate in this study at multiple research sites in Africa, including up to 40 KIs such as yourself. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Before you decide if you want to participate in this study, we want you to learn more about it. This consent form gives you information about this study. Study staff will talk with you and answer any questions you may have. Once you understand the study and its requirements, you can decide if you want to take part in it. If you decide to participate in this study, you will sign your name or make your mark on this form. A copy of this document will be offered to you.

Your eligibility to participate in this study will then be assessed, and once confirmed, you will be considered enrolled in the MTN-041 study.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see “Your Rights as a Research Participant/Volunteer” section for more information).

WHAT IS THE PURPOSE OF THIS STUDY?
You are being asked today to take part in MTN-041. The main goal of this study is to better understand what may affect the use of two safe and effective HIV prevention methods, a vaginal ring (VR) and an oral tablet, by pregnant and breastfeeding women in Africa. To do this, study staff will ask your personal views, and what you think about women using vaginal products and oral medications during pregnancy and breastfeeding.

MTN-041 KIs will be asked to participate in an in-depth interview (IDI).

STUDY PRODUCTS
No study products (investigational drugs or other products) will be tested in this research study.

STUDY PROCEDURES
The MTN-041 study consists of one study visit, which starts today after you sign this informed consent form. Additional visit(s) may be conducted to complete all required procedures, if necessary. Visits will take place here at this study clinic or at a place agreed upon by you and the study staff, which may be your home or another convenient location ***[SITE TO INCLUDE ALTERNATE LOCATION]*.**

The procedures done at this visit will take about ***[SITE TO INSERT TIME]***.

- Study staff will ask you where you live and other questions about you, and your understanding of the study requirements.
- You will complete one or more written questionnaires where you will be asked some general questions, such as your age, education, living situation, working situation, relationship status, and health.
- You will be asked to have an IDI:
    - You will have an IDI in the presence of one or two MTN-041 research staff members. The IDI will take approximately ***[SITE TO INSERT TIME]***.
    - The interviewer(s) will talk with you about the two safe and effective HIV prevention methods of interest.
        - Daily oral tablet called Truvada, which is approved for pre-exposure prophylaxis (PrEP) to prevent HIV infection in multiple countries.
        - Monthly VR containing dapivirine, which is being considered for approval to prevent HIV infection in multiple countries.
    - The interviewer(s) will talk with you about various topics related to the use of vaginal products and oral medications by pregnant and breastfeeding women. The interviewer(s) will also talk with you about common beliefs and practices related to pregnancy, childbirth and breastfeeding, including specific practices you might encourage or discourage, and about possible educational and marketing approaches to promote use of vaginal and oral HIV prevention methods during pregnancy and breastfeeding.
    - The interviewer(s) will then ask more questions, may take notes, and will audio-record your conversation to make sure we record your words exactly how you said them.

- Study staff will also:
    - Inform you about other available health and social services, if needed.
    - Schedule your next visit, if necessary.
    - Reimburse you for your visit(s).

RISKS AND/OR DISCOMFORTS

During the interview, you may be asked some questions or have some conversations that cause you to feel embarrassed or uncomfortable. Trained study interviewers will help you deal with any feelings or questions you have. You can choose not to answer questions or leave the room during the interview at any time.

Another possible risk of this study is loss of confidentiality of the information you give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, interviews will take place in private, and the information recorded during your interview will be strictly protected. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. This means that no one other than the MTN-041 interview team will be able to link your responses to you personally. The audio recordings and any information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-041 study team for the purposes of this research.

It is possible that others may learn of your participation here and treat you unfairly or discriminate against you because of it. For example, you could have problems getting or keeping a job, or being accepted by your family or community. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS

There are no direct benefits to participating in this study. However, you and others may benefit in the future from information learned in this study. Participants in this study may also appreciate the opportunity to contribute to HIV prevention research efforts, including future research of HIV prevention products for pregnant and breastfeeding women. Information participants provide may help researchers improve counseling materials about product use and sexual behavior. Lastly, findings from this study may help health professionals improve communication and understanding between researchers and participants in HIV prevention studies.

Medical care for HIV infection and other health conditions will not be part of this study. This study cannot provide you with general medical care, but study staff will refer you to other available sources of care, if needed.

NEW INFORMATION

You will be told of any new information learned during this study that might affect your willingness to stay in the study. You will also be told when study results may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT
You may be removed from the study early without your permission if:

- The study is cancelled by the US NIH, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB) or Ethics Committee (EC). An IRB is a committee that watches over the safety and rights of research participants.
- You are unwilling or unable to comply with required study procedures, including study visit attendance.
- Other reasons that may prevent you from completing the study successfully.

COSTS TO YOU
There is no cost to you for study related visits.

REIMBURSEMENT
[*SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT*]: You will receive ***[SITE TO INSERT AMOUNT $XX]*** for your time, effort, and travel to and from the clinic at each scheduled visit.

CONFIDENTIALITY
Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- RTI International
- Site IRBs/ECs
- FHI 360
- Representatives of the US Federal Government, including the US OHRP, NIH and/or contractors of NIH, and other local, US or international regulatory authorities
- Study monitors
- Study staff

The researchers will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY
[SITE TO SPECIFY INSTITUTIONAL POLICY]: It is unlikely that you will be injured as a result of study participation. If you are injured, the ***[INSTITUTION]*** will give you immediate necessary treatment for your injuries. You ***[WILL/WILL NOT]*** have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. NIH does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER
Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study,

you will not lose the benefit of services to which you would otherwise be entitled at this clinic. If you want the results of the study after the study is over, let the study staff members know.

PROBLEMS OR QUESTIONS
If you ever have any questions about the study, or if you have a research-related injury, you should contact ***[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]*** at ***[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]***.

If you have questions about your rights as a research participant, you should contact:***[INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]*** at ***[INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER]***.

SIGNATURES- VOLUNTARY CONSENT

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC]:

If you have read this consent form (or had it read and explained to you) and if you understand the information and voluntarily agree to take part in the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

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