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Narratives from Women using the Dapivirine Vaginal Ring in an Open Label Extension Study

By

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AUTHOR'S DECLARATION

I, the undersigned, declare that the work in this document is my own original work and that I have not previously submitted it to any university for a degree. The papers presented here originated from a study that was implemented at multiple sites in sub-Saharan Africa including the Centre for the AIDS Programme of Research in South Africa (CAPRISA), where I was actively involved in study implementation. This included creation of study documents, facilitating regulatory approvals, maintenance and storage of study data, scheduling participants, creation of the study visit flow, reviewing of qualitative transcripts and quality control activities. In addition, I was involved in the data analysis using the Dedoose software to create the code book, code transcripts, observe key themes and preparation of the summaries of emerging themes. All material herein contained has been duly acknowledged where applicable.

Kalendri Naidoo

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DEDICATION

For my son, Thyushan Naidoo.

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I am sincerely thankful to all the women that participated in this study and the study staff at the sites that implemented the research.

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To my family – Thank you for the support, encouragement, care, understanding and patience. I am forever grateful.

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ABBREVIATIONS AND ACRONYMS

AGYM	Adolescent Girls and Young Women
AHA	Adherence in HOPE and ASPIRE
AIDS	Acquired Immunodeficiency Syndrome
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CATALYST	Catalysing Access to New Prevention Products to Stop HIV
CD	Compact Disc
CRF	Case Report Form
DREAM	Dapivirine Ring Access and Monitoring
FGD	Focus Group Discussion
FHI360	Family Health International
GCP	Good Clinical Practice
HOPE	HIV Open-label Prevention Extension
HIV	Human Immunodeficiency Virus
IDI	In-Depth Interviews
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IR	Incidence Rate
MOSAIC	Maximizing Options to Advance Informed Choice for HIV Prevention
MTN	Microbicides Trials Network

NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
OLE	Open Label Extension
PREP	Pre-Exposure Prophylaxis
QC	Quality Control
RDL	Residual Drug Level
RTI	Research Triangle Institute
STI	Sexually Transmitted Infection
UKZN BREC	University of KwaZulu-Natal's Biomedical Research Ethics Committee
UN	United Nations

SUMMARY

In sub-Saharan Africa, women and girls represented 63% of new Human Immunodeficiency Virus (HIV) infections in 2020. Adolescent girls and young women (AGYW) aged 15–24 years are twice as likely to be living with HIV as compared to young men. Therefore, efforts to develop and roll out safe, effective and acceptable HIV prevention products for women, are continuing. An important example of a female-initiated HIV prevention strategy is the dapivirine vaginal ring which showed a 27% reduction in HIV-1 incidence in the Microbicides Trials Network (MTN)-020/A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) study and by 31% in the International Partnership for Microbicides (IPM)-027 The Ring study. The dapivirine vaginal ring was subsequently tested for safety and adherence in the Open Label Extension (OLE), MTN-025/HIV Open-label Prevention Extension (HOPE) study.

The MTN-032/Adherence in HOPE and ASPIRE (AHA) study was a two-phase exploratory sub-study of the ASPIRE (AHA part 1, after ASPIRE and before HOPE study initiation) and HOPE (AHA part 2, after HOPE was completed) studies which utilised single qualitative in-depth interviews (IDIs) to explore social conditions and issues related to participation around the use of the dapivirine vaginal ring as well as suitable approaches to market the study product. I report on the narratives from women participating in the AHA study (Part 2) within the context of known safety, partial product efficacy and choice, focusing on what motivated women to join the HOPE OLE study, women's understanding of the vaginal rings' efficacy, how they understood it to work in their bodies to prevent HIV and barriers and motivators to vaginal ring adherence.

Narratives echoed previous research findings about ring experiences however some important differences were noted – motivations to join research did not necessarily translate to vaginal ring use, although it was only partially efficacious women still chose to use it for protection and even though women had a choice to decline the vaginal ring, they still opted to accept it but ultimately had challenges with use. The key points from the narratives are indicative of an ecological model where both individual levels of influences and social environmental levels of influences impacted decisions and actions when it came to study participation and ring use. The urgent need to address these influences through concomitant interventions that speak to the multiple levels of influence will support an individual's use of and adherence to HIV prevention products.

Although HIV prevention research amongst women has progressed substantially over the years, important biomedical, behavioural, and social science factors still play a role in the prevention of HIV infection among women globally. Addressing and understanding these factors together with the provision of current and future HIV prevention options to women will result in a global decline of HIV infections among women and progression towards the United Nations (UN) goal of ending the AIDS epidemic by 2030.

CHAPTER ONE

1. General Introduction

1.1 Human Immunodeficiency Virus (HIV) in sub-Saharan Africa

Even though it has been more than forty years since HIV was first detected, it is still rampant amongst populations around the world. Globally, there are about 38 million people living with HIV/Acquired immunodeficiency syndrome (AIDS) and about 1.5 million people newly infected with HIV in 2020 (1). In sub-Saharan Africa, women and girls represented 63% of new HIV infections in 2020 (Figure 1, Figure 2) (1, 2). Adolescent girls and young women (AGYW) aged 15–24 years are twice as likely to be living with HIV as compared to young men (1). Limited ability to negotiate for safer sex practices and the presence of gender-based violence, early sexual debut, age disparate relationships and challenges with mutual monogamy have all contributed to the disproportionate burden of infection in female populations (3, 4). Therefore, the continued efforts to develop and roll out safe, effective and acceptable HIV prevention products for women, are critical.

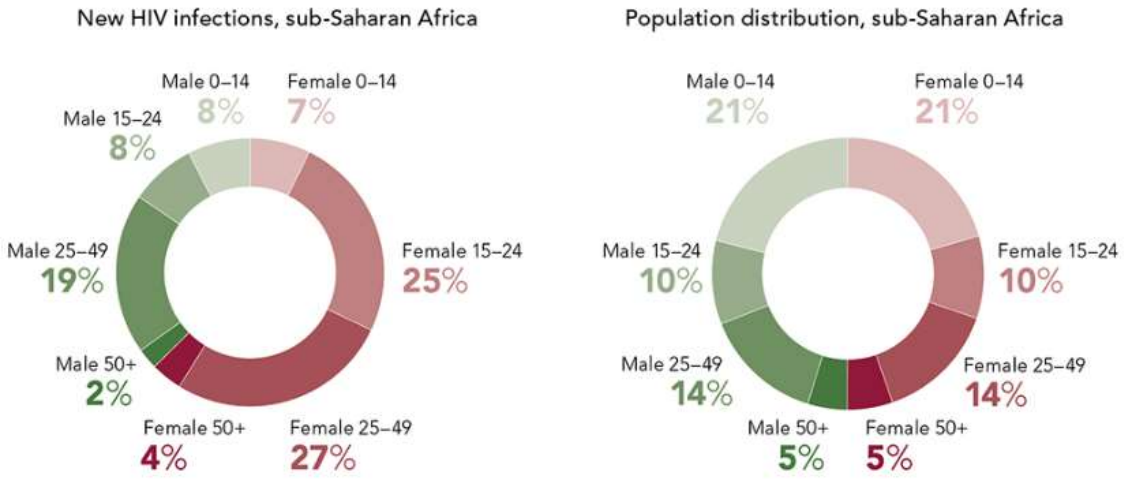

Figure 1: New HIV infections in sub-Saharan Africa by age and sex in 2020

(Source: Geneva: Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2021. https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf)

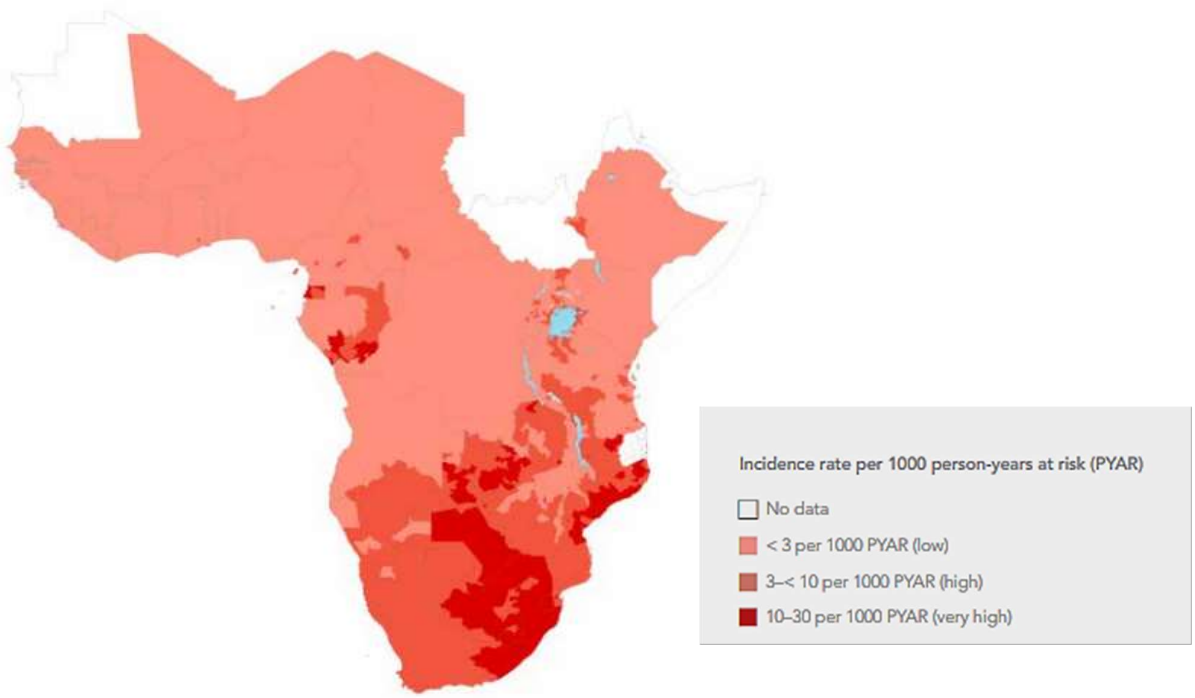

Figure 2: HIV incidence in sub-Saharan Africa among adolescent girls and young women (aged 15-24 years) in 2020

(Source: Geneva: Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2021. https://www.unaids.org/sites/default/files/media_asset/JC3032_AIDS_Data_book_2021_En.pdf)

1.2 Dapivirine Vaginal Ring

An important example of a female-initiated HIV prevention strategy is the dapivirine vaginal ring. Dapivirine, a substituted diaminopyrimidine derivative, is a tight binding non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent antiviral activity against HIV-1. NNRTIs bind allosterically to the HIV-1 reverse transcriptase enzyme preventing viral replication and therefore production of infectious virus. The dapivirine vaginal ring is an off-white flexible ring containing 25 mg dapivirine and was designed to provide sustained release of dapivirine for a minimum of 28 days, to provide for a longer duration dosing schedule that is less burdensome to end-users, when compared to coitally-dependent vaginal HIV prevention strategies, condoms, or oral Pre-Exposure Prophylaxis (PrEP) (5, 6). Data of dapivirine residual levels in

used vaginal rings indicate that approximately 4mg of dapivirine is released over a 28-day period of ring use (5, 6). When delivered via a vaginal ring, dapivirine has demonstrated favourable safety and pharmacokinetic profiles (5, 6).

Two completed phase III trials, MTN-020/A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) (5) and International Partnership for Microbicides (IPM)-027 (The Ring Study) (6), evaluated long-term safety and efficacy of the 25 mg dapivirine vaginal ring.

The first, ASPIRE (5), was a phase III, randomized, double-blind, placebo-controlled trial which tested the dapivirine vaginal ring among healthy, HIV-negative, sexually active women between the ages of 18 and 45 years in Malawi, South Africa, Uganda and Zimbabwe from August 2012 through to June 2015. From the 5516 women who were screened, 2629 were enrolled. Of this, 1313 were in the dapivirine group and 1316 were in the placebo group. Participants used the vaginal ring for one month before it was replaced with a new ring. From the 168 HIV-1 infections that occurred, 71 were among those assigned the dapivirine vaginal ring and 97 were among those assigned the placebo vaginal ring (incidence 3.3 and 4.5 per 100 person-years, respectively). The dapivirine vaginal ring arm showed a 27% reduction in HIV-1 incidence overall and a 37% reduction when data was analysed excluding two study sites with lower retention and adherence (5).

The second, The Ring Study (6), was a multicentre, randomized, double-blind, placebo-controlled, phase III trial that involved healthy, HIV-negative, sexually active women who were enrolled at seven research centres in South Africa and Uganda. Of the 1959 participants that were enrolled in the trial,1307 participants were randomly assigned to the dapivirine group and 652 to the placebo group. In the dapivirine group, 77 participants underwent HIV-1 seroconversion during 1888 person-years of follow-up (Incidence Rate (IR) = 4.1 per 100

person-years), as compared to the placebo group where 56 participants underwent HIV-1 seroconversion during 917 person-years of follow-up (IR = 6.1 per 100 person-years). HIV-1 infection was lower in the dapivirine group by 31% as compared to the placebo group (6).

The dapivirine vaginal ring was subsequently tested for safety and adherence in multi-site, Open Label Extension (OLE), phase III studies initiated in 2016 – MTN-025/HIV Open-label Prevention Extension (HOPE) (7) and IPM-032/Dapivirine Ring Access and Monitoring (DREAM) (8). HOPE was conducted between July 2016 and October 2018 and enrolled 1,456 women at former ASPIRE trial sites in Malawi, South Africa, Uganda and Zimbabwe (7). The HOPE sample size was dependent upon how many former ASPIRE participants were interested in participating and met the inclusion criteria. The inclusion criteria included previously enrolled in ASPIRE, able and willing to provide written informed consent, able and willing to provide adequate locator information, HIV-uninfected, using an effective method of contraception at Enrolment, and intending to use an effective method for the duration of study participation and agreed to not participate in other research studies involving drugs, medical devices, vaginal products, or vaccines for the duration of study participation (7).

Women who enrolled in HOPE could choose to accept or decline the dapivirine vaginal ring at any time and continue in the study. Women were followed for one year, with monthly visits for the first three months, and quarterly visits thereafter reflecting a shift to a more real-life type of setting where the participants knew they were receiving an active product that has been shown to be safe and effective when used as directed.

DREAM was conducted between July 2016 and January 2019 and enrolled 941 former participants of The Ring Study at sites in South Africa and Uganda (8). Unlike HOPE, DREAM only enrolled women who agreed to use the vaginal ring during the study. In both studies,

used vaginal rings were collected and tested for residual drug levels (RDL). Overall, 90% of used vaginal rings in HOPE (7) and 95% of used vaginal rings in DREAM (8) showed that they were used although consistent use could not be confirmed.

The MTN-032/Adherence in HOPE and ASPIRE (AHA) study was a two-phase exploratory sub-study of the ASPIRE (AHA part 1, after ASPIRE and before HOPE study initiation) and HOPE (AHA part 2, after HOPE was completed) studies. The AHA study utilised single qualitative in-depth interviews (IDIs) or focus group discussions (FGDs) to explore social conditions and issues related to participation around the use of the dapivirine vaginal ring as well as suitable approaches to market the study product. More details on the MTN 032 AHA study is provided in Chapter 2.

1.3 Narratives from Women using the Dapivirine Vaginal Ring

For this thesis, I report on the narratives from women participating in the AHA study within the context of known safety, partial product efficacy and choice focusing on what motivated women to join the HOPE OLE study, women's understanding of the vaginal rings' efficacy, how they understood it to work in their bodies to prevent HIV and barriers and motivators to vaginal ring adherence.

Altruism, personal benefits, financial interests and contributing to advancing research have been reported in literature as the most common reasons for participating in clinical trials (9, 10). Some women from ASPIRE reported using the ring for altruistic reasons and felt part of a team contributing to science (11, 12). OLE studies provide an extended continuum of care often in resource limited settings where participants can retain access to the study product during multinational regulatory submission and review processes. They likewise access the

other healthcare benefits that a research or OLE study offers. The design of an OLE study compared to a randomised placebo-controlled trial is however fundamentally different, and the reasons why women are motivated to join these two types of research may also be different or may be similar. For example: does feeling at risk for HIV translate into motivations to use a HIV prevention product and motivations to join HIV prevention research regardless of whether it is a HIV prevention clinical trial or an OLE study?

In the paper presented in Chapter 3 (Women's Motivations for Participating in the Dapivirine Vaginal Ring Open Label Extension Study), I aimed to first understand the reasons women from ASPIRE were motivated to join HOPE, an OLE study, and whether this was linked to having access to an effective HIV prevention product, i.e., the dapivirine vaginal ring.

It has been shown that people's belief in product efficacy stems from their desire to want to prevent HIV and even when informed that a product is still investigational, they want to believe it can protect against HIV (13, 14). In a qualitative sub-study of ASPIRE participants, where preferences for product formulations were assessed, biological efficacy and safety were associated with the method of administration and delivery, formulations administered into the circulatory system were described as providing high protection due to flow of the drug in the entire body (15).

In the paper presented in Chapter 4 (Efficacy and Action of the Dapivirine Vaginal Ring as Understood by Women Participating in an Open Label Extension Study), I aimed to understand women's perceptions of product efficacy during HOPE knowing the partial efficacy of the vaginal ring and how they understood the vaginal ring to work to prevent HIV.

Correct and consistent use of an HIV prevention product is important and necessary, for it to be effective however the decision to use an HIV prevention product can be influenced by many community, social, economic and individual factors (11). Non-adherence reported by participants during the ASPIRE trial included removing the vaginal ring briefly for sex or bathing and multiple day removals during menses (11). Cleaning the ring, worries that the vaginal ring would hinder the flow of menstrual blood and menstrual discomfort aggravated by the vaginal ring were reported as reasons for removals during menses (11). Older women (22 – 45 years of age) mentioned side effects from vaginal ring use, such as vaginal discharge and itching, womb pain and headaches (11). Besides the high adherers (defined as consistent use at every visit measured), all other participants, regardless of age, cited fear of partner disapproval to the ring, mostly during sex, as the primary reason for non-use (11). Hygiene concerns, outside influence from peers and family members and interest in study benefits were the other reasons reported for non-use (11).

During HOPE, of 14,463 vaginal rings dispensed, 14,270 (99%) were returned and 14,034 (97%) were tested for residual levels of dapivirine (7). RDL testing showed that 89% (12,530/14,034) of vaginal rings had levels consistent with at least some use and some vaginal rings (<10%) appeared not to have been used (7).

Many HIV prevention studies have adopted similar adherence approaches with an emphasis on teaching, providing information, and the use of positive support, and responsibility to promote “perfect” adherence (16). However, for some studies estimated product use still varied among participants and was lower than expected (16) to provide protection.

In the paper presented in Chapter 5 (Qualitative Perceptions of Dapivirine Vaginal Ring Adherence and Drug Level Feedback Following an Open-Label Extension Trial), I examined

self-reported behaviours with adherence among women who had used the active vaginal ring during HOPE to understand adherence challenges within the context of more “real world conditions” and the known efficacy of the dapivirine vaginal ring.

1.4 Study Rationale

Biomedical technologies ultimately rely on individual human behaviour to be effective, and behaviour is driven by one’s knowledge, beliefs, attitudes, perceptions and influences. Additionally, individuals are residing within social and environmental contexts which includes family, peers, community members, work, religion, cultural and socio-economic factors and influences. In public health research and programs, interventions that rely on behaviour change (e.g., consistently adhering to ring use) will theoretically help individuals live a healthy lifestyle and reduce disease risk. However, making individual-level behaviour changes is not simple because Individual beliefs, attitudes, perceptions and the immediate and surrounding environmental influences are complex. Consequently, if the context within which individuals exist is not addressed, understood correctly, or accommodated in a culturally appropriate manner, behaviour changes to improve health outcomes will remain a challenge.

This thesis explores the complex behaviour of individuals in the context of using biomedical HIV prevention strategies in phased research stages with the intention to better understand how beliefs, attitudes, perceptions and social environmental factors impact decisions around health improvement and health behaviour change. Data from qualitative analysis methods are an important way to measure and understand the nuances behind human behaviour, and how they interact with each other, and change over time. This information will give researchers, program implementers, policymakers and advocates insight about addressing attitudes, beliefs and behaviours that can be used in the development and implementation of future HIV prevention products and studies.

1.5 Objectives

The motivation to join a research study may not necessarily be related to having access to an HIV prevention product (e.g., oral PrEP, ring). Further, an individual's perception of efficacy of the HIV prevention product itself may or may not result in consistent product use. Women's self-report of adherence behaviours tells the story of how behaviours and other factors contribute to the complex experience of participating in an OLE study and using the dapivirine vaginal ring.

Based on this, the following objectives were developed:

- To explore women's motivations for joining HOPE – an OLE study (Chapter 3).
- To evaluate women's understanding of product efficacy and how the vaginal ring worked in their body during an OLE study (Chapter 4).
- To explore reasons for product adherence/non-adherence, following presentation of HOPE residual drug level results (Chapter 5)

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CHAPTER TWO

2. Methods

2.1 MTN 032 Study Summary

The MTN 032/AHA study and all associated research tools were approved by local Ethics Committees at all the research sites i.e., Lilongwe, Malawi; Durban (2 sites) and Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe. In addition, the data analysis under this Degree was approved by University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (BREC) (BREC/00001487/2020). The AHA study timelines are reflected in Figure 3.

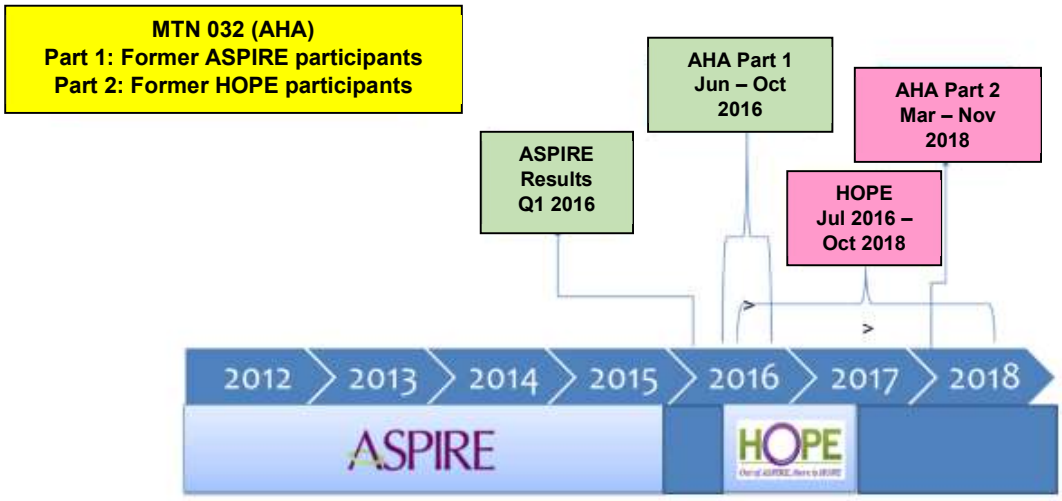

Figure 3: Study implementation timelines

Recruitment and accrual for part 1 took approximately 4-6 months at each research site and part 2 approximately 9-12 months at each site. In part 1 of the AHA study, 187 former ASPIRE participants with variable levels of adherence to the dapivirine vaginal ring were enrolled from seven of the ASPIRE trial sites based in Lilongwe, Malawi; Durban (2 sites) and Johannesburg, South Africa; Kampala, Uganda; Chitungwiza, Zimbabwe and Milton Park, Zimbabwe. In part 2 of the AHA study, which is the focus of this thesis, 60 former HOPE

participants with variable levels of adherence were randomly selected at six of the HOPE sites based in Lilongwe, Malawi; Durban (2 sites) and Johannesburg, South Africa; Kampala, Uganda and Chitungwiza, Zimbabwe. Part 2 explored both female participant and male partner attitudes toward the ring. Specifically, female IDIs examined the effect of known efficacy on product use. Other aspects, such as women's motivation to enrol and continue study participation, the impact of the knowledge of the vaginal ring's efficacy on ring acceptance, marketing and roll-out were also explored.

2.1.1 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the study ensured a standardised approach across all research sites in determining participant eligibility and producing reliable data. To ensure that these criteria were met, rigorous quality control checks were in place to review and verify the eligibility criteria of each participant prior to enrolment.

Part 2 Inclusion Criteria

- Participation in the HOPE study.
- Able and willing to provide written informed consent.
- Able and willing to complete the required study procedures.

<u>For participants who did not acquire an HIV infection while taking part in HOPE:</u>

- Evidence of vaginal ring dispensation for at least three consecutive months.

<u>For participants who acquired an HIV infection while taking part in HOPE:</u>

- Evidence of vaginal ring dispensation in the month before the participant's acquisition of HIV.

Part 2 Exclusion Criteria

- Has any significant medical condition or other 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.

2.1.2 Study Implementation

Procedures for the study were developed at a multisite and site level to ensure standardized data collection and procedures were compliant with Good Clinical Practice (GCP) guidelines and the study protocol. Prior to study implementation, site teams (including myself) completed extensive protocol trainings and created study documents (informed consents, tools, checklists and other forms). Separate training sessions were held where mock sessions of IDI's and FGD's were done and interviewers were trained on interviewing techniques including probing skills, active listening, open ended questioning, reading body language and remaining neutral.

2.1.3 Study Procedures

Study procedures comprised of administrative, regulatory and behavioural components as described in Table 1.

Table 1: Screening and enrolment procedures for MTN 032/AHA part 2 participants

Component	Procedures
Administrative and Regulatory	• Confirm eligibility • Informed consent for part 2 screening and enrolment (Appendix I) • Verify eligibility • Collect demographic information • Collect locator information • Provide reimbursement
Behavioural	• Administer behavioral questionnaires and tools • Conduct IDI using guide (Appendix II). Conducted in a semi-structured format, audio-recorded, and written notes taken during the interview. • Complete debrief report

Following confirmation of eligibility criteria, informed consent and demographic and behavioral questionnaires were administered by trained study staff. IDIs were then conducted in the language of the women's choice (English or local language) using a semi–structured interview guide (Appendix II). Women were reminded that the interview was about their experience during HOPE, it was confidential and questions/concerns could be raised at any time. IDIs were audio-recorded, transcribed and translated into English (if conducted in a local language) with quality control checks completed by local site staff, including comprehension of local terminology.

2.1.4 Data Management and Quality Control

After the completion of the visit: The participants file would then undergo quality control (QC) steps to ensure that all procedures were completed, and data was collected as per protocol. In addition, on the same day as the interview, the Interviewer would verify that the audio recorder properly recorded the session. The audio file was copied onto the password-controlled computer at the site.

Within one week following the interview: Once all Case Report Forms (CRF's), tools and the debrief reports were reviewed for accuracy and completeness, sites would then upload them to the RTI via a secure server. The audio file was saved onto a compact disc (CD) as source documentation of the interview. The CD was labelled and filed in the participant's binder.

Within one month following the interview: The audio-file was used to translate and transcribe the discussion. All transcripts were translated and transcribed (when conducted in a local language) in English unless there were distinctive local language phrases that needed to be conserved. The English transcript was uploaded to RTI via a secure server.

Site Transcript QC Process: Quality checks of the translation/transcription were performed at the site. A second staff member (not the translator of the interview) that was fluent in the local language would listen to the complete audio file while reading the English transcript to determine that the quality of translation is sufficient. These reviews were done in three batches until the quality was acceptable for each translator/transcriber. Systematic quality checks were also completed by listening to at least three, 5-minute parts per interview of the audio file and comparing it to the transcript. Additionally, the text of each transcript was reviewed for completion, content clarity and errors.

2.2 Data Analysis

A codebook (Appendix III) was developed with codes (“parent code”) and sub codes (“child codes” based on the research questions from this study and previous studies of similar research (1, 2). Each code and subcode had a definition of its meaning to guide the coding staff in its consistent application. Table 2 below displays an excerpt of the codebook, including the definitions. The coding structure reflected the topics/themes covered in the interview guides. However, provision was made for adding new and unexpected codes, and a “parking lot” code for data that was perceived as important but did not have a pre-designated code. Therefore, new codes that developed from the analysis that were not previously identified were iteratively added and the codebook and code definitions were modified accordingly. Once finalized, the codebook was used for coding of all the transcripts with the codes being applied to the applicable theme in the textual data using the Dedoose software (Version 8.1.8). Following this, interpretation of the coded data and salient themes were described in summary memos.

The coding process involved a core group of analysts, including myself, who discussed the codebook and application of the codes during the coding process through emails, teleconference and in person meetings. Intercoder consistency was confirmed at a level above a mean kappa score of 0.70 for 10% of transcripts among the coders. After this process, the coding inconsistencies were discussed and resolved through agreement amongst the coding team. Frequent discussions among the coding team ensured that coding remained uniform and authentic.

Table 2: Excerpt from the MTN 032/AHA part 2 codebook

Parent Code	Child Code	Definition
ADHERENCE		Code anything not already under the child codes about adherence to the ring.
	INITIATION/FIRST USE	Anything about initiating ring use, either at the beginning of ASPIRE, HOPE, or after a period of dis-use. Include discussion about getting used to the ring, any issues, or lack of issues.
	USE	[About physically using/not using the ring]. Anything about using the ring or not using the ring. Include instances of removals (e.g. to clean or show others) or persistence with ring use and inserting/replacing the ring every month. Use this code for ring removals if the intention is to still use the ring (remove for less than a day). Use the DISCONTINUATION code if she talks about intentionally stopping ring use.
	BARRIERS	Apply when participant describes barriers she experienced during the HOPE trial to using the ring consistently. Include any difficulties with using the ring and how overcame these barriers. Double code with REMAIN or RISK as needed. For hypothetical barriers to using the ring in the future use FUTURE code.
	MOTIVATIONS/ SUPPORT	Apply when participants describe any motivations or reasons they are able to adhere to the ring or change her ring use (or things they think could have helped during HOPE trial), including any support she received from others, tools or reminders used to remember to change the ring, or a personal sense of altruism to use the ring for the benefit of other women/society. Double code with appropriate PEOPLE codes as needed. For hypothetical motivations or support for using the ring in the future use FUTURE code.
	DRUG FEEDBACK	Apply to discussion around her individual drug level results. Include what her results were and what they mean to her (how she understands them) as well as how important it was to her to receive a certain level (0-3).
	(DIS)AGREEMENT	Use for whether the participant agrees or disagrees with the results (i.e. whether they match how she remembers using the ring or not). (Child code of DRUG FEEDBACK)
	DRUG TESTING	Use for whether she trusts the method of testing the ring or not and any complaints about the timing of getting the results back. (Child code of DRUG FEEDBACK)
	DISCONTINUATION	Code any discussion of discontinuing ring use, due to voluntary or clinical reasons for shorter or long periods, with the intention of stopping ring use (even if she later changes her mind), for a minimum of a day. May include pregnancy, HIV sero-conversion, etc. If discussing thoughts about the study ending, use the TRIAL code. Use the USE code instead for instances of removal where she still intends to use the ring.

This thesis used primary data to do a secondary analysis on women's narratives during participation in the HOPE OLE study regarding motivation to join a research study, perception of efficacy and product-use adherence, themes that are discussed in detail in the three papers that follow.

MTN 032/AHA part 2 data transcripts were analysed to explore the following thematic areas. The codes that were used to filter transcripts for these themes are indicated in the methods section of each paper.

- Motivations for joining HOPE including HIV worries (Chapter 3).
- Descriptions of how women thought the vaginal ring worked in their body and their understanding of its efficacy (Chapter 4).
- Reported reasons for product adherence/non-adherence following presentation of residual drug level results (Chapter 5).
- Reactions to and understanding of their drug level results from HOPE (Chapter 5).
- Whether women trusted the method used to test the vaginal ring (Chapter 5).

2.3 Limitations

There are limitations to this research that should be taken into consideration. The data collected is only from a sub-set of women from HOPE, randomly selected based on their Month 1 adherence (low, middle and high release) using a 1:3:1 ratio and therefore may not fully reflect the ring-use experiences of all women participating in HOPE. Further, the interviews were conducted 0 – 9 months after women exited the HOPE study, so recall bias must be considered when interpreting the data and women may have provided socially desirable responses during the IDI's. The scope of the analysis did not include cultural diversities among each country/site and its impact, if any, on the results. In addition to their extended exposure to clinical trial participation and use of the study product, there were in-

person interviews and hard-copy materials that could have affected each women's experience and product acceptability/use which may have been further influenced both in positive and negative ways by their social networks, households, partners, families, friends, communities and waiting room discussions.

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CHAPTER THREE

Paper 1:

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Title: Women's Motivations for Participating in the Dapivirine Vaginal Ring Open Label Extension Study.

Authors: Kalendri Naidoo; Elizabeth T Montgomery; Ariana WK Katz; Morgan Garcia; Sarita Naidoo; Leila E Mansoor

Women's Motivations for Participating in the Dapivirine Vaginal Ring Open Label Extension Study

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Women's Motivations for Participating in the Dapivirine Vaginal Ring Open Label Extension Study

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SHORT TITLE: Motivations for Participating in an Open Label Extension Study

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ABSTRACT

Open-Label Extension (OLE) studies are important in the drug development process and are used to further support the licensing applications and regulatory approvals of products. We aimed to understand why women chose to join the HOPE OLE study -- where women were offered the dapivirine vaginal ring after two pivotal trials were completed -- through data collected from individual in-depth interviews. Ten women at each of the six HOPE research sites in Lilongwe, Malawi; Durban (2 sites) and Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe, were enrolled (n = 60). Access to an effective user-initiated HIV prevention product was one of the main reasons women joined HOPE. Although many participants worried that their male partners might expose them to HIV, they chose to remain in their relationships and avoid conflict or confrontation with their partners by discreetly using the ring to protect themselves. Other reasons for joining were quality healthcare, reimbursement and altruism. Researchers should better understand social and personal motivators behind research participation in order to recognize community sociocultural norms and its influences on product acceptability and adherence challenges.

KEYWORDS: women, dapivirine vaginal ring, motivation, HIV prevention

INTRODUCTION

After the dapivirine vaginal ring was shown to reduce the risk of HIV-1 acquisition in two phase III trials, by 27% in MTN 020/ASPIRE which was conducted from 2012 to 2015 (Baeten et al., 2016) (Figure 1) and by 31% in The Ring Study which was conducted from 2012 to 2016 (Nel et al., 2016)), it was further for long term safety and acceptability in two OLE studies which were implemented from 2016 to 2018, i.e., MTN-025/HOPE (Baeten et al., 2021) (Figure 1) and IPM 032/DREAM (Net et al., 2021). Data from OLE studies are important in the drug development process and are used to further support the licensing applications and regulatory approvals of products. During 2021 - 2022, the dapivirine vaginal ring was approved as an HIV prevention option for women in South Africa, Zimbabwe, Kenya, Uganda and Lesotho (Atieno, 2022; Fokazi, 2022).

As part of understanding women's experience with vaginal ring use and study participation, the MTN-032 Assessment of ASPIRE and HOPE Adherence (AHA) sub-study was implemented post-ASPIRE in 2016, and post-HOPE in 2018 (Figure 1), and used qualitative interviewing methods with participants who exited each of these trials (Montgomery et al., 2018, 2021; Naidoo et al., 2021). One of the objectives of MTN-032/AHA was to understand the reasons why participants in ASPIRE chose to join the OLE study, HOPE, and have access to the dapivirine vaginal ring.

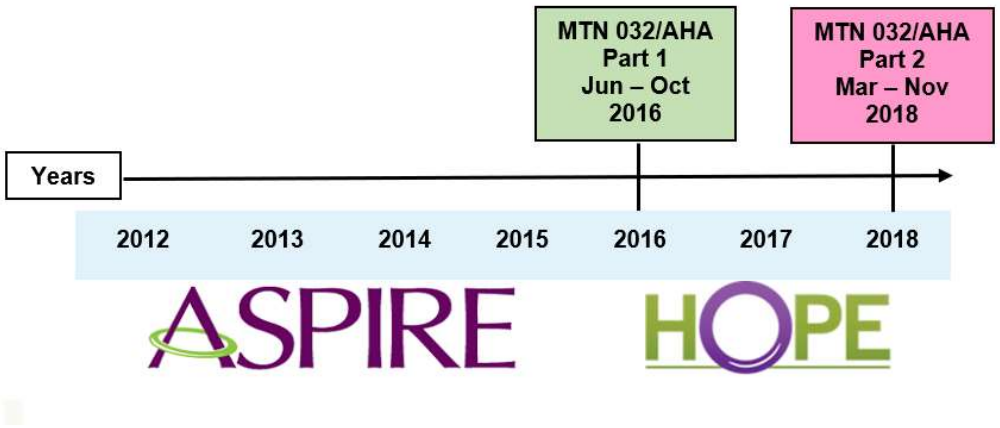

Figure 1: Study implementation timelines

Motivations to join HIV prevention studies can be divided into social benefits such as altruism and personal benefits such as HIV protection, access to healthcare and financial reimbursement (Dhalla & Poole, 2011). The most common reason for joining HIV prevention studies has been reported as altruism and protection against HIV (Colfax et al., 2005; Dhalla & Poole, 2011; Dubé et al., 2020; Sullivan et al., 2020). Speaking to the altruistic motivator among volunteers during pre-trial community education sessions could aid in recruitment. Protection against HIV may be indicative of the need to have a product that is acceptable and easy to access and use however understanding the efficacy of the products should be addressed among volunteers and participants.

Access to healthcare and financial reimbursement has been reported as motivators (Colfax et al., 2005; Katz et al., 2019), which is expected since most HIV prevention studies are conducted in low- and middle-income countries with over extended health care systems that have the highest HIV burden (UNAIDS Data, 2021). These two motivators have been controversial among the research community as they are seen as undue inducement in impoverished countries where this research is being conducted (Emanuel et al., 2005) versus

reasonable benefits that volunteers directly gain in these same impoverished countries for their contribution through study participation (Haire & Ogundokun, 2014; Halpern et al., 2004).

For this analysis, we aimed to understand why women chose to join the HOPE study – a new, post-trial OLE study where women were offered an active ring with known efficacy. This information will aid in understanding how women's motivations for joining an HIV prevention OLE study might be the same or different from a placebo-controlled clinical trial, offering insight into women's priorities at different stages of the biomedical product pipeline and roll-out. This will help with study recruitment strategies, highlight important topics that should be addressed during education sessions, improve community sensitization and recognize any links between motivations for study participation and product adherence and acceptability.

METHODS

Parent trial: The HOPE study evaluated the safety and adherence of the dapivirine vaginal ring among eligible HIV-negative former ASPIRE participants (Baeten et al., 2021). Women could choose to accept the ring or not at any point during their participation in HOPE. Study follow-up visits occurred monthly for the first three months and thereafter quarterly with the option of visiting the site monthly to pick up a new ring.

Ancillary Study: The AHA qualitative study was implemented from March 2018 to November 2018 and enrolled former HOPE participants who chose to use the ring during HOPE and agreed to be contacted for future studies. Potential AHA participants were contacted in sequential order from a randomized list generated by the HOPE Statistical Center for HIV/AIDS Research and Prevention (SCHARP). Ten women at each of the six HOPE research sites in Lilongwe, Malawi; Durban (two sites) and Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe were offered participation in AHA, 0 – 9 months after they had exited HOPE.

Following the review and confirmation of eligibility criteria, the informed consent and demographic and behavioral questionnaires were administered by trained study staff. A once off, in person individual in-depth interview (IDI) was then conducted in the language of the women's choice (local African language or English) using a semi–structured interview guide (Appendix I) by female study staff trained in behavioural interviews and techniques. Discussions were facilitated around reasons for joining and remaining in HOPE, benefits gained from the study or from using the ring and any concerns about participation. Women were reminded that the interview was confidential and questions could be raised at any time.

IDIs were audio-recorded, transcribed and translated into English (if conducted in a local African language) and thereafter quality control processes were completed with local site staff, including comprehension of local terminology. Transcripts were then uploaded to Dedoose (Version 8.1.8), a qualitative software programme, for Data Management including coding, which allowed the raw contextual data to be reviewed and summarized with its meaning extracted. Analysts, including the lead author, used an iteratively developed codebook (Appendix II) to descriptively code for key themes and topics.

The codebook was adapted from similar previous research studies (Montgomery et al., 2018) and corresponded to the thematic areas covered in the IDI guide, allowing space for unanticipated themes to emerge. The codebook contained parent codes, with subcodes, that were defined by the lead author and analyst team. Refinements to code assignment were discussed throughout the process to maintain consistent interpretation and application of thematic meaning, and to develop or expand codes to accommodate emergent ideas. The coding and analysis approach for this paper was thus primarily thematic and focused on data coded assigned with the parent code of "trials" and "HIV" and the related sub-codes, "join/remain", "social/emotional impact", and "risk", respectively. Intercoder consistency was

confirmed at a level above a mean kappa score of 0.70 for 10% of transcripts across five coders and code application questions were discussed and resolved with the coding team.

The AHA study protocol was approved by the Institutional Review Boards at RTI International, and at each study site and regulated by the U.S. National Institutes of Health and the Microbicide Trials Network.

RESULTS

Sixty women were enrolled into MTN-032/AHA with two women not being included in the analysis due to inappropriate enrolment, resulting in an analytic sample of n=58. Detailed characteristics of the study sample have been presented previously (Naidoo et al., 2021). Women averaged 32 years of age (range 23–48), and less than half (44.8%) reported being married, 84.5% reported having the same partner since exiting HOPE, but 66.1% did not know whether their partners had other sex partners. Less than half of the women (41.1%) did not know their partner's HIV status and 74.5% were worried about acquiring HIV in the next 12 months.

HIV Protection

Most women did not have any concerns about joining HOPE due to their previous experience with participation in ASPIRE; especially knowing that they were being provided with the active ring containing dapivirine. The primary reason reported by several women for enrolling in the HOPE study was the desire for a user-controlled HIV prevention method to manage their perceived risk due to distrust of their male partners and inconsistent use of condoms. They stated that the ring offered them protection against HIV since it was proven to be efficacious.

> *"My reason for the joining HOPE was the ring and the fact that I have used it before.. It sometimes happened that in that particular day I was not going to use a condom, but*

I would know that there is an alternate prevention method inside of me, that would protect me." (Durban, South Africa)

This woman specifically notes that her concern is exacerbated by expected behavioral norms within a relationship with her primary partner. Besides the distrust, she cannot ask him to use condoms as he is her primary partner.

"My protection is complicated, ask me why… I don't know how my partner behaves. So I may not have other sexual partners but he may have other partners. So what can I do for him? Can I tell him to use condoms? He is my permanent partner so I can't." (Kampala, Uganda)

Additionally, for some women, joining HOPE gave them rapid access to using the ring again, which was a strategy that offered the benefit of discreetly maintaining protection against HIV that would serve their children's wellbeing and avoid arguments with their husbands. Avoiding conflict in the relationship and finding a means to protect themselves was viewed as the easier option rather than confrontation with the partner.

"So, I realized that if I managed to join HOPE I would insert my ring and I would avoid conflict with my husband. I would just use it quietly to ensure I'm protected so as to care for my children." (Chitungwiza, Zimbabwe)

Access to Counseling and Healthcare

Receiving counselling, education and additional healthcare services – such as testing and treatment for sexually transmitted infections (STI's), HIV testing, pap smear screening, physical examinations and contraceptive provision – were also discussed by many women as additional motivators for joining and was seen as a benefit that they received throughout their participation in the study.

"We also received counselling and [were] educated about other things that we did not know. Things about life and about engaging in sex. Things that you were not aware

are happening and things that you did not take note of, you were just doing them. We received additional education about things that we did not know." (Durban, South Africa)

"I gained many things because they were testing us for HIV, sexually transmitted infections and cervical cancer screening." (Lilongwe, Malawi)

A few women favorably compared the services received at the study site to local healthcare facilities. Women mentioned the good quality of care that was provided by study staff and that they had trust and confidence in the study staff to help them without judgement when they felt unwell and required treatment.

"If you've got a problem like STI's and things like that you get help from this clinic. Sometimes at the local clinic we are sometimes scared to tell the nurses that "okay this is what I have" and things like that but here you know that everything that happened here stays here, it's confidential between you and study staff." (Durban, South Africa)

Two women from Lilongwe, Malawi, further spoke about how the counselling, education and frequent HIV testing they received during HOPE resulted in sexual behaviour changes. This woman reports that went from having multiple sexual partners to just one sexual partner based on the counselling she received at the site.

"The other thing was the counseling and the love that you show us here… you are loving people and well behaved. This helped me change my behavior and as I am talking now, I only have one sexual partner." (Lilongwe, Malawi)

The second woman reported a similar behavior change in her male partner when he realized she was being tested for HIV during her study visits, indicating that she believed that her HIV status, whether negative or positive, was reflective of his sexual behaviour:

"Before I joined, my partner was having multiple sexual partners but when I started participating here, I was encouraging him that "look, this is my status. We have not been trusting each other because of your behavior." It turned out that he started changing his behavior after realizing that I get tested and I am HIV negative. I benefitted because he changed his behaviour and he is now a good man." (Lilongwe, Malawi)

Financial Reimbursement

Some women candidly discussed how they joined for the reimbursement that was provided for their time spent during clinic visits. These women spoke about needing the money for their children's school fees or essential food items. Others went on to explain that some women joined for the reimbursement, but others joined because they wanted to use the ring.

"Some were just coming here to get the ring because they knew that at the end of the day they would be given transport money which they would use at their homes but they had no passion to consistently use the ring so that it can give good results." (Lilongwe, Malawi)

"We came for different reasons, some people came to get money and some really had the passion and love for the ring." (Durban, South Africa)

Altruism

Many women spoke about altruism and joining the study for the betterment of future generations of women, their children and grandchildren and that they would have another option for HIV prevention available to them. They reported being proud to be part of the study and that it gave them a purpose.

"It was because women had been left behind when it comes to fighting HIV. Our prevention methods were fewer than those for men….. But at least if we get another

option of using a vaginal ring which we can insert and no one gets to know that you have it is something that motivated me to join the HOPE study." (Kampala, Uganda)

"Your expected results it's like you get so much pleasure from doing that and you always feel proud of what you are doing, who you are. Remember what I had in mind when I started I was not doing this for myself only. I have a son, I still want more children. So do I want them to come in this world and next thing they pass-on because of HIV? No, at least they must have options, you know? I will know that I was part of getting those solutions on the table." (Johannesburg, South Africa)

Support from Partners, Family and Friends

Several women mentioned that their partners knew about their participation and supported them. Their partners' encouragement helped them make the decision to join and enable them to continue participating.

"I told him the benefits that we get here. I told him that "we get tested for HIV each scheduled visit that we go, they also screen us for other diseases; a thing that cannot be happening if we go to other health facilities." So, he understood it and accepted that I should join." (Lilongwe, Malawi)

Some women opted to discuss their decision to join with their family, friends and neighbours, whilst others chose to make the decision on their own and join without anybody knowing. One woman mentioned that when she discussed joining HOPE with other former ASPIRE participants, they mentioned that they did not want to join the HOPE study because they were provided with the placebo ring in ASPIRE, perhaps indicating some distrust towards clinical research or blame on researchers for assigning them to the placebo arm.

"I even asked that 'Remember we first joined without knowing whether it had medicine or not and now you have realized that what you had didn't have medicine but in case you had one with medicine would you still decline?' and some would say 'If I had used

one with medicine I would join but now that I used one without medicine I will not join.'"(Kampala, Uganda)

DISCUSSION

The reasons reported by former ASPIRE clinical trial participants for electing to join the HOPE OLE study and use the ring – access to good healthcare, protection against HIV, financial reimbursement and altruism – were similar to the findings of previous research about why participants chose to join HIV prevention clinical trials (Colfax et al., 2005; Katz et al., 2019; Sullivan et al., 2020).

Access to an effective user-initiated HIV prevention product was one of the main reasons women joined HOPE. This allowed women achieve an important health goal of protecting themselves against HIV. Although many participants worried that their male partners might expose them to HIV, they chose to remain in their relationships and use the ring to protect themselves. Financial stability and material support provided and offered by male partners may contribute to women's decision or inability to leave problematic partnerships, especially in low- and middle-income countries (Warren et al., 2018; Psaros et al., 2018). Additionally, sociocultural norms in communities may also play in women remaining in challenging relationships. Male partners may perceive condom use as signaling a lack of trust, intimacy and love in the relationship (Mash et al., 2010) and women may feel that discussions around condom use could result in arguments, physical violence and a breakdown in the relationship (Hlongwa et al., 2020). Participants' choice to access the ring rather than risk a confrontation with their partner about possible unfaithfulness or condom use highlights how some women utilize user-initiated HIV prevention methods to navigate sexual relationships from a position of less power than their male partners.

Access to good healthcare was seen as a benefit to joining HOPE. Public healthcare facilities in sub-Saharan Africa provide limited medical care due to numerous factors, including staff shortages, poor financing, insufficient resources and inadequate systems and processes (Gold & John, 2013). For this reason, women sought the quality healthcare that was being offered through participation in the HOPE study and voiced their gratitude. Women directly benefitted from the healthcare and counselling that was provided during the HOPE study just as they benefitted from having the choice of an HIV prevention method. Researchers debate on whether providing medical benefits during studies may be seen as undue inducement (Haire & Ogundokun, 2014; Mfutso-Bengo et al., 2008; Mngadi et al., 2017) however the provision of healthcare is an essential requirement in these low- and middle-income countries. When research studies are being implemented, the location and resources should be considered (Dainesi & Goldbaum, 2011) and engagement between researchers, stakeholders and communities is encouraged to look at a long-term plan for the provision of quality healthcare where possible and feasible.

Some women openly discussed that financial reimbursement was the motivation for women joining the HOPE study. Participants were reimbursed as per the local country regulations in both ASPIRE and HOPE. Monetary payments for participation in a study have been reported to increase a person's willingness to participate (Almeida et al., 2007; Bentley & Thacker, 2004; Colfax et al., 2005). Reimbursement can be seen as an incentive motivator to join research studies however further internal interventions are needed to ensure adherence to the study products after joining the study. In OLE studies, a "real-world" type of setting is created similar to attending local healthcare providers and thus, the need for reimbursement in this sort of setting is debated (Mngadi et al., 2015). Researchers consulted with local Ethics Committees, Community Advisory Boards and other country regulators throughout study implementation to ensure that participants are compensated appropriately for their time, inconvenience and travel as per most country regulatory authorities. Thought and care must be taken when research is being conducted in countries where poverty is high and the reason

for the financial reimbursement should be explained thoroughly to study participants throughout study participation.

Even though altruistic motivations in clinical research can sometimes be intertwined with personal benefits, altruism has come up often as a motivator to participation in HIV prevention research (Dubé et al., 2020). Several women portrayed a sense of pride when they reported that they were motivated to join so that their children and future generations of women would benefit. Many women have been affected by HIV in some way, whether among their own family members and friends or within their communities. This could be the driving force behind their altruistic motivations. Altruism can be aligned with what scientific research aims to accomplish – a treatment, cure or prevention that can be used in future – especially in OLE studies where the study product is known to be efficacious.

Discussions with male partners, families and communities and their support in the decision to join the HOPE study and use the ring were important for some women. This is an important point that can be used for future marketing of the ring – in that it can be seen as a shared HIV prevention responsibility in relationships (Montgomery et al., 2021), can be used by your peers and communities or can be used by yourself autonomously and discreetly.

A small minority of women reported that others felt discouraged as they received the placebo product in ASPIRE and did not want to join HOPE for this reason. These women seemed resentful towards researchers providing them with the placebo product and perhaps needed further clarification during the informed consent process on the design of clinical trials and randomization versus an OLE study in order to make an informed decision about joining HOPE.

There are limitations to this research that should be taken into consideration. The data collected is from a sub-set of women from HOPE. Our sub-sample was randomly selected to

minimize the risk, however, their perspectives and knowledge may not be reflective of the same from the full cohort of HOPE study participants, nor of the broader scope of women who were in ASPIRE and did not elect to join HOPE, nor of African women from these settings who may have been eligible, but did not join these studies. Further, the concepts explored in this analysis are complex and may not have been adequately understood by study participants. Comprehension and wording in interview guides were extensively shared across study sites and pre-tested to minimize misunderstanding. Further, our study relied on participants' availability and interest to spend approximately 90 minutes participating in an interview, which may have introduced limitations, and the study relied on participants to comment on attitudes of acceptability and product use experiences with a research study team, which may have resulted in social desirability bias. The interviews were conducted after women exited the HOPE study, which may have minimized a desire to report "favorable" responses but may have introduced recall or other biases. The scope of the analysis did not include cultural diversities among each country/site and its impact, if any, on the results. It must also be considered that these women participated in both ASPIRE and HOPE resulting in them having access to the benefits of quality healthcare, reimbursement and the study product over a long period of time.

The social and personal benefits offered from clinical trials prior to efficacy determination versus OLE studies seem to be viewed equally by participants. Women were motivated to join HIV research to reduce their HIV risk and take control of their health. If participants are receiving benefits through study participation such as quality healthcare and reimbursement, that are not coercive, these should be considered acceptable because of the participants contribution to science. HIV research is ongoing among important populations in low- and middle-income countries and access to quality healthcare through study participation should in turn motivate local leaders to focus on health system strengthening where women have access to quality healthcare on a daily basis and not just through clinical trials. Researchers should better understand social and personal motivators behind research participation in order

to recognize community sociocultural norms and its influences on product acceptability and adherence challenges.

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DECLARATIONS:

Conflicts of Interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Author contributions:

Kalendri Naidoo was involved in the study implementation at the study site, data collection, data interpretation, data coding and analysis and writing this article. Elizabeth T. Montgomery was involved in the study design, overall study implementation, data interpretation and article review. Sarita Naidoo was involved in the study design, overall study implementation and article review. Ariana W.K. Katz was involved in the study design, oversaw study implementation, data coding and analysis, data interpretation and article review. Morgan Garcia was involved with overall study implementation and article review. Leila E. Mansoor was involved with study implementation at the study site, data collection and article review.

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Ethics approval: The MTN 032 study protocol was approved by the Institutional Review Boards at RTI International, and at each study site and regulated by the U.S. National Institutes of Health and the Microbicide Trials Network**.**

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: All participants were informed that any publication of this study will not use their name or identify them personal.

Availability of data and material: The data will not be available to the public. If an individual is interested in exploring the data, they should contact the lead author.

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APPENDIX I: MTN 032/AHA Study Part 2 Female In-depth Interview Guide

MTN-032 Part 2

Female In-depth Interview (IDI) Topic Guide

INSTRUCTIONS for the Interviewer: How to use the IDI Guide

1. Section topics are in shaded in gray and **bolded**.
2. *Instructions/suggestions to interviewer are in italics and [brackets].*
3. Not ALL questions need to be asked. It is up to the interviewer's discretion if a question should be skipped if the participant has already provided a response to the question earlier in the interview. Please ensure that by the end of the interview, all the topics and key themes have been covered.
4. Purpose statements should be considered notes to the interviewer and are not meant to be read aloud. They explain the reason for asking that question or set of questions in order to provide more context to the interviewer who can then rephrase in her own words or clarify to the participant as necessary.
5. There are two levels of questions:
    a. Primary interview questions: appear in **bold** text. They address the topics that you as the interviewer should ask and discuss with participants. You are not required to read them verbatim, but they are written to ensure some consistency across IDIs.
    b. Probing topics are indicated with a bullet. If you find that the participant does not provide much information in response to the primary question, these probing topics may be used to encourage further discussion. Probes with the words "*KEY PROBE*" written before it are probes that are the most important to try to address. Depending on what has already been discussed, and the IDI context, you may or may not ask the rest of the probes.
6. Words found in (parentheses) are meant to provide wording options to interviewers to fit various situations. For example, they often provide a present or past tense verb.
7. The IDI guide is not meant to be used to take notes. Rather, you should use the separate notes form, where you will also insert your initials, the participant's PTID, as well as the date, start and end time of the interview.
8. **Special note about seroconverters:** It is important for study staff to review the participant's HIV status before conducting any study procedures. When asking questions to seroconverters, start off by emphasizing that confidentiality is maintained in the study and reassure the participant that her study information will not be shared with anyone outside the study. Then inform the participant that you are aware that she has seroconverted.

Before starting the IDI, ensure the participant has provided written informed consent.

[*Start Recorder and Read Introduction*]: **My name is _____. Thank you again for your willingness to be in this study. The main goal of this discussion is to better understand your experience participating in HOPE. I want to remind you that there are no right or wrong answers, and what we discuss here will be kept confidential; we will not share your personal information or responses with anyone outside of the study.**

If during our discussion, there are issues or concerns that you would like to talk about, feel free to bring them up; I will take note of them and answer them directly after the interview. If I cannot answer them, I can refer you to someone who may be able to help. Before we start, can you confirm for the recorder that you have already provided written informed consent to take part in this discussion? [*Wait for oral confirmation to begin*].

A. Motivation for joining HOPE

Purpose: To get details about all of the reasons why she joined HOPE and whether she was influenced more from the ring or the study benefits.

1. **What are the reasons why you joined HOPE?**

Possible probing topics:

- *KEY PROBE:* What were you hoping to gain from HOPE? Did you get what you came for? Please explain.
- *KEY PROBE*: Did you join HOPE more because of the ring or more because of the benefits you received from the study? Please explain.
- *KEY PROBE*: What concerns did you have about joining HOPE?

2. **How important did you feel it was to discuss whether to join HOPE with someone else? Why?**

Possible probing topics:

- *KEY PROBE*: With whom did you actually discuss? Why? How did they react?
- *KEY PROBE*: How did you get them to accept your decision to participate (if applicable)?
- *KEY PROBE*: How did their opinions influence your decision?
- Why did you not discuss with (others not mentioned above)?

3. **How has being part of HOPE affected you emotionally or socially?**

Possible probing topics:

- How has being in HOPE made you feel about yourself? (describe feeling and if positive or negative?) Why?
- Tell me about any positive or negative social experiences. (What happened, why, how did you feel? Etc.)

B. Ring Efficacy

Purpose: Find out her current understanding of how the ring works with different types of use and how that influenced her ring use.

4. **I know you were told how to use the ring, but now I want to know in your own view how you THINK you need to use the ring to get your desired level of protection from HIV?** *(e.g. only when going to have sex, throughout the full month, intermittently depending on whether you feel at risk, etc.)* **Please explain.**

Possible probing topics:

- *KEY PROBE*: How are these beliefs the same or different from how you actually used the ring in HOPE?
- *KEY PROBE***:** What are other ways of using the ring that you heard about?

5. Did you think you needed to be protected all the time in HOPE? Please explain.

Possible probing topics:

- *KEY PROBE:* How did this influence your use of the ring? (*i.e. did you keep it in all the time even if you didn't feel you needed protection? or did you remove at times when you didn't feel like you needed protection?)*
- *KEY PROBE:* If you took the ring out to have sex for a few hours, how protected would you feel? Please explain.
- *KEY PROBE:* If you took the ring out and didn't have sex during that time, how protected would you feel the next time you had sex? Please explain.
- *KEY PROBE:* If you removed the ring to clean it, how protected would you feel the next time you had sex? Please explain.

6. How do you think the ring works in your body?

Possible probing topics:

- How fast do you think the ring provides protection after insertion?
- How fast do you think your protection decreases after removing?
- When you think about the drug in your body, how does that make you feel?
- How well do you think the ring protects against HIV?
- Do some people need more or less drug to be protected?
- What do you think affects how much drug is in one person's body compared to another person?

C. Drug results; Adherence/non-adherence; Ring influence on sexual activity

Purpose: To explore her reaction and understanding of her drug results from HOPE and explore the factors that influenced the participants' adherence or non-adherence in HOPE.

We would like to look at all of your results throughout HOPE and discuss them with you. Here are your results… [*Present over-time tool*]

7. How do you feel about these results?

Possible probing topics:

- What do these results mean to you?
- Do these results match with how you remember using the ring throughout HOPE? Why or why not? [*record on PSF if matches/does not match*]
- Do you trust the method used to test the rings? Why or why not? [*record on PSF if trusts/does not trust*]

8. Tell me about your sex life while in HOPE.

Possible probing topics:

- How many sexual partners did you have while in HOPE? (Same or different as in ASPIRE?)
- What kind of partners were they (*i.e. primary, casual, client, etc*.)?
- What kind of sex did you have with each partner (vaginal, anal, oral)? How often?
- What kind of sex did you have during menses?

9. Women differ in whether they feel comfortable talking to their partners about the ring. What did your partner(s) know about the ring, if anything?

Possible probing topics:

- Did you tell your partner(s) or how did he find out?
    - How did you bring it up?
    - How did he react?
    - How did his reaction affect your use of the ring?
    - Did his feelings about the ring change over time? What caused the change?

10. How did the ring affect your sexual life, if at all?

Possible probing topics:

- *KEY PROBE*: How did the ring affect sexual pleasure? (for you and your partners)
- *KEY PROBE*: Did you or your partner ever feel the ring during sex? Please explain a situation when this happened.
- *KEY PROBE*: How did your partner influence your ability to use the ring?
    - Did you sometimes remove the ring for sex? If yes, why? If no, why not?
    - If removed for sex, where did you put it? When did you re-insert the ring?
    - Did you do anything to avoid feeling the ring during sex? [*Ask about sex positions or acts;* foreplay/finger]
- If there were changes in your sex life, do you think they were good or bad? Why so?

11. What were the barriers to using the ring consistently?

Possible probing topics:

- *KEY PROBE*: [*If applicable*] How did it make you feel when you had a "0", "1", or "2"?
- *KEY PROBE*: When was it the hardest to use the ring? Why? What did you do to overcome the barriers?
- *KEY PROBE*: What kept you participating in HOPE despite the barriers you experienced?
- *KEY PROBE*: What motivated you to use the ring despite the barriers you experienced?
- *KEY PROBE*: How at risk did you feel during these times (when not having a 3)? Why?
- How did receiving 3 rings affect your ability to use the ring? (e.g. easier or harder) Why?

[NOTE: If participant consistently had 2's and/or 3's, ask question 12, otherwise skip to Section D.]

12. What was motivating you to use the ring during this time? (e.g. desire to protect yourself from HIV, desire to help the community)

Possible probing topics:

- *KEY PROBE*: [*If had any 3's*] How did it make you feel when you had a "3"?
- *KEY PROBE*: [*If had any 2's*] How did it make you feel when you had a "2"? Why?
- *KEY PROBE*: When was it hard to sustain this level of protection? Why? What did you do to overcome the barriers?
- Did you ever remove the ring during this time, even though you achieved "2's" and "3's"?
- How important was it to you to see high protection levels? Why was it so important?

D. Participant Engagement Activities & Study Procedures

Purpose: To gain insight on usefulness of site engagement activities at improving adherence.

13. What clinic events did you participate in during HOPE? *(e.g. group adherence meetings, social events, waiting room discussions, etc.)*

Possible probing topics:

- How often did you attend the events? [Be specific about what the event was.]
- What did you hear or talk about during the events with other participants? Describe what came up.
- What was it like to interact with staff during these events?
- What was it like to interact with other participants?
- Did you discuss what occurred during the events with other participants or other friends/family/members of community?
- What other activities you would have liked to have been offered?
- What did you hear from staff or others about ring use at your clinic?

14. How did the clinic events influence your ring use and/or feelings about the ring?

Possible probing topics:

- How were the activities helpful or not helpful in addressing:
  - Yours or other participants' perceptions of ring?
  - Yours or other participants' worries (side effects, harm) about the ring?
  - Trust or mistrust of medical research or healthcare?

E. Ring acceptability

15. What is your current opinion of the dapivirine ring? [U*se opinion tool*]

Possible probing topics:

- All the things you disliked (and why)?
- All the things you liked (and why)?
- How did your attitudes about the ring change over time in HOPE?
- What would make you like it more?
- What is your primary partner's opinion of the ring?
- What were the attitudes of other participants while in HOPE? How did this affect your thoughts about the ring?
- What were the attitudes of other people you told about your ring? How did this affect your thoughts about the ring?

F. HIV Worries and HIV Protection

Purpose: To gather more in-depth information about her HIV risk perception and risk reduction strategies.

16. How worried were you about getting HIV while in HOPE?

Possible probing topics:

- KEY PROBE: What increased or decreased your worry in HOPE? (e.g. *multiple partners, ring use, condom use, seropositive partner, drug/alcohol use, receiving money/goods for sex, HIV testing, etc.*)?
- *KEY PROBE*: How do your worries about HIV compare to other worries in your life (*e.g. financial, work, partner relationship, family issues, etc.*)?
- *KEY PROBE*: How did your concern about HIV affect your ring use?

17. What are you doing to protect yourself from HIV now that HOPE has ended? (*e.g. condoms, HIV testing, PrEP, medical male circumcision, mutual monogamy, etc.*)

Possible probing topics:

- *[Skip for seroconverters]* Do you think you will get HIV? Why/why not?
- How motivated are you to stay HIV free?
- *KEY PROBE*: What do you think about waiting for the ring to be approved by your government before it is available to you?
- Are you more worried about getting HIV from your primary partner or from someone else? Please explain.

G. Ring uptake, marketing and product roll-out

18. We hope the ring will be widely available in the future. If it is, what would make you interested in using it? *[Skip for seroconverters]*

Possible probing topics:

- *KEY PROBE*: What percentage of protection/ efficacy would the ring need to provide in order for you to use it in the future?
- *KEY PROBE*: How would you prefer to use the ring (e.g. wear at certain times or all the time)?
- What support would you need to help you use it?
- Where would you want to get the ring?

19. What about others – if the ring is widely available, what do you think will be important to others to make them want to use it?

Possible probing topics:

- What would encourage their interest and make the ring appealing to them?
- Do you think it will be popular – with whom?
- What concerns would they most likely have?
- What advice would you give to overcome these concerns?

H. Wrap Up and Closing Remarks

20. We have talked about a lot of things today. Thank you for taking the time to talk to me and share your opinions. We truly appreciate your willingness to participate and discuss your experience with us. You've been with us for a long time now – so many years -- and we are grateful for your commitment to this research and to helping us move the ring forward in science. Before we end, I want to give you the chance to tell us anything else you think we should know about the ring – good things, bad things, challenges with using it – anything, that will help us better understand the truth about this ring.

21. Do you have any questions for me?

APPENDIX II: MTN 032/AHA Part 2 Codebook

Parent Code	Child Code	Definition
TRIALS		Anything about the ASPIRE or HOPE trials including her experience as a trial participant. Anything about the ASPIRE results or thoughts or feelings about HOPE ending, or differences between ASPIRE and HOPE. Include anything they reported that happened between ASPIRE and the start of HOPE. Use this code when comparing differences between ASPIRE and HOPE study design or procedures.
	JOIN/ REMAIN	Discussion around participants' motivation to join and remain in HOPE. Include any discussion about joining or remaining for the ring, incentives -- monetary or health -- or any other. Include discussions about joining with others and about why she continued to participant despite barriers to ring use or lack of support. Double code with BARRIERS, SUPPORT or appropriate PEOPLE code as needed.
	SOCIAL/ EMOTIONAL IMPACT	Anything about how being in HOPE made the participant feel internally (emotionally) about themselves or how it affected them socially, including feelings about receiving their drug feedback. Also include discussion about feelings of altruism for joining the study or being a participant in the study. Include positive or negative experiences or feelings.
	ACTIVITIES	Anything about HOPE-organized activities such as tea parties, workshops, outreach events, male partner activities, etc. designed to address participant adherence and retention. Include discussion about the events influencing ring use or feelings about the ring. Includes description of actual or desired community engagement and education activities.
	CLINIC/ VISIT	Anything to do with the ASPIRE/HOPE clinic environment in general. Include anything with attendance or lack of attendance of ASPIRE/HOPE visits, keeping/missing appointments, duration of visits. Include discussions of monthly or quarterly visits.
	SITE-LEVEL FEEDBACK	Use for discussions about the feedback sites gave participants about the overall site's adherence performance (not individual results) in ASPIRE or HOPE. Use for discussions about receiving interim HOPE results as well.
RING		Anything about the ring that is not previously covered under the child codes. If discussing how the ring changed sex life, double code with SEX. Include discussion around storing rings at home or issues storing rings at home.
	EFFICACY	Apply to discussions of product efficacy, either actual, perceived, or desired including when a participant talks about feeling protected from the ring. Should be used to capture discussions about how she thinks she needs to use the ring to get the protection she desires.
	MECHANISM OF ACTION	Apply to discussion about how participants think the ring works to prevent HIV, including how it works in her body or others' bodies. Use when participant talks about how quickly or slowly the ring provides protection before insertion and after removal.
	OPINION NOW	Anything about anyone's opinions (her or her partner or family/friends, etc.) about the ring NOW (at time of interview) including its characteristics, fear/ring worries about the ring, likes and dislikes.

Parent Code	Child Code	Definition
	OPINION PAST/ OVERTIME	Anything about anyone's opinions (her or her partner or family/friends, etc.) about the ring over-time (prior to time of interview) including its characteristics, fear/ring worries about the ring, likes and dislikes.
	SIDE EFFECTS/ PHYSICAL SAFETY	Apply to comments specifically about side effects and perceived side effects relating to the product from anyone who was exposed to the ring. Include discussion about physical safety of the ring including how the drug in her body makes her feel. If relates to feeling protected or being safe from HIV, code as EFFICACY.
	FUTURE	Code any discussion regarding willingness or plans to use (or not use) product in the future, in general not specific to any study. Include information about where they would want to get the ring in the future and how much they would be willing to pay and how often they would like to use the ring (all the time or intermittently). Include discussions about wanting to be (or suggestions on who should be) an advocate or champion for the ring. Include any recommendations or thoughts on who else would use or benefit from the ring if the ring became successful and what would make the ring appealing for others to use it as well as what concerns others may have about using the ring. Also include discussions about more general thoughts about the future post-trial.
ADHERENCE		Code anything not already under the child codes about adherence to the ring.
	INITIATION/FIRST USE	Anything about initiating ring use, either at the beginning of ASPIRE, HOPE, or after a period of dis-use. Include discussion about getting used to the ring, any issues, or lack of issues.
	USE	[About physically using/not using the ring]. Anything about using the ring or not using the ring. Include instances of removals (e.g. to clean or show others) or persistence with ring use and inserting/replacing the ring every month. Use this code for ring removals if the intention is to still use the ring (remove for less than a day). Use the DISCONTINUATION code if she talks about intentionally stopping ring use.
	BARRIERS	Apply when participant describes barriers she experienced during the HOPE trial to using the ring consistently. Include any difficulties with using the ring and how overcame these barriers. Double code with REMAIN or RISK as needed. For hypothetical barriers to using the ring in the future use FUTURE code.
	MOTIVATIONS/ SUPPORT	Apply when participants describe any motivations or reasons they are able to adhere to the ring or change her ring use (or things they think could have helped during HOPE trial), including any support she received from others, tools or reminders used to remember to change the ring, or a personal sense of altruism to use the ring for the benefit of other women/society. Double code with appropriate PEOPLE codes as needed. For hypothetical motivations or support for using the ring in the future use FUTURE code.

Parent Code	Child Code	Definition
	DRUG FEEDBACK	Apply to discussion around her individual drug level results. Include what her results were and what they mean to her (how she understands them) as well as how important it was to her to receive a certain level (0-3).
	(DIS)AGREEMENT	Use for whether the participant agrees or disagrees with the results (i.e. whether they match how she remembers using the ring or not). (Child code of DRUG FEEDBACK)
	DRUG TESTING	Use for whether she trusts the method of testing the ring or not and any complaints about the timing of getting the results back. (Child code of DRUG FEEDBACK)
	DISCONTINUATION	Code any discussion of discontinuing ring use, due to voluntary or clinical reasons for shorter or long periods, with the intention of stopping ring use (even if she later changes her mind), for a minimum of a day. May include pregnancy, HIV sero-conversion, etc. If discussing thoughts about the study ending, use the TRIAL code. Use the USE code instead for instances of removal where she still intends to use the ring.
HIV		Anything about HIV or AIDS. Includes HIV testing outside of the trial setting. Use TRIALS if talking about HIV testing in ASPIRE/HOPE.
	RISK	Any discussion of perceived vulnerability of HIV and risk behavior or situations, including sexual risk, multiple partners, partner has other partners, other risk behavior (drugs/alcohol, pregnancy risk), unknow HIV status of partner or risk in general (i.e. having a reckless behavior, or being in a risky situation). Includes perceived lack of risk. Also includes discussion about HIV worries, including what influenced worry and timeline or changes in level of worry (before HOPE, after, etc.). If talking about feeling protected from the ring, use EFFICACY. The risk does not have to be blatantly identified by the participant, can be interpretative by coder. Double code with appropriate PEOPLE codes as necessary.
	PREVENTION METHODS	Anything about methods she is using, has used or plans to use to prevent HIV besides the ring or in combination with the ring. Could be male or female condom, or other methods i.e. oral PrEP, monogamy, regular testing, etc. Also includes all practical aspects of condom use (i.e., use/non-use, storage, transport, etc.), preference for ring and/or other products.
HEALTH		Anything about health not related directly to the ring (if ring related use SIDE EFFECTS/ PHYISCAL SAFETY). Includes anything about sexual and reproductive health, menses, and fertility.
CONTEXTUAL / STRUCTURAL		Include discussion of the social, cultural or structural context in which the participant is living. May include local practices, urban/rural location, HIV prevalence, sociocultural norms, religion, local beliefs, traditional medicine, interaction with local clinics or non-study healthcare (including healthcare staff), or other discussions of the community. Include anything about employment (including sex work), work, school, studies, domestic work, etc. Use also for anything in place before the trials began (e.g. cultural aversions to trials overall).

Parent Code	Child Code	Definition
STIGMA/ MISCONCEPTIONS		Anything about any kind of rumors, gossip, stories (positive or negative), or stigma about research in general, ARVs, condoms, HIV prevention, HIV transmission, the HOPE study in particular (e.g. associated with Satanism or Witchcraft) or the ring or its formulation (e.g. it causes cancer). Include discussion about foreign researchers or white researchers as it applies to HOPE. Applies to external and internalized stigma/misconceptions.
SEX		Anything about her sex life, sexuality, sex practices (oral, vaginal or anal) or behaviors, including how the ring affected the sexual experience. Include comments about experience of discomfort or pain during sex and any mention of participant or partner either feeling or not feeling the ring during sex. Any comments about experience of pleasure during sex, either positive or negative. Any change in sexual practices as a result of ring use (different position, avoiding oral or digital sex, etc.). Applies to either her or her partner's experience.
DISCLOSURE		Anything about disclosing trial participation, product use/non-use, drug feedback results, or HIV status to anyone. Also includes disclosing information about relationships and sex partners. Include discussions of honesty, dishonesty, lying, secrecy, or hiding something. Double code with appropriate PEOPLE codes as necessary.
PEOPLE		Anything about groups of people who DO NOT fall into the child code categories (e.g. boss, coworkers, etc.). Include community groups that one may be a member of. If coworkers or boss, double code with CONTEXTUAL/STRUCTURAL.
	COMMUNITY / NEIGHBORS	Anything about neighbors or members of the community
	FAMILY	Anything about immediate or extended family members. Double code with PEERS if their family member is also a participant.
	MALE PARTNERS	Anything about male partners – husbands, boyfriends, casual partners. Include number, type, communication, and decision-making power, relationship dynamics, trust, etc. Double code with MOTIVATION/SUPPORT if partner helped her adhere to ring.
	PEERS	Include fellow participants and other friends not in the study, including housemates who are not family members. Anything about other women in the ASPIRE or HOPE trials. Include discussion/conversations with other participants before/during/after trial, in the waiting room, etc. Should be applied to specific discussions of other participant actions, conversations, etc., not to the general 'we'. Double code with FAMILY if their family member is also a participant.
	STAFF	Anything about HOPE and/or ASPIRE staff.
OPINION TOOL		Use for any discussion during the opinion tool (emoji stickers) activity.
VULVA/PENIS MODELS		Use for any discussion when the vulva puppets or penis models are used or discussed.

Parent Code	Child Code	Definition
SEROCONVERSION		Anything about the participant's personal experience sero-converting, including how one sero-converted, timing, and reaction.
PARKING LOT		Anything that does not fit into the above codes but we think may be a salient theme. To be discussed during coding calls regularly.
STAR		Star quote or star examples.

CHAPTER FOUR

Paper 2:

Title: Efficacy and Action of the Dapivirine Vaginal Ring as Understood by Women Participating in an Open Label Extension Study.

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ORIGINAL PAPER

Efficacy and Action of the Dapivirine Vaginal Ring as Understood by Women Participating in an Open Label Extension Study

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Abstract
The concept of efficacy, and how HIV prevention products biologically work can be complex. We report on women's interpretation of efficacy of the dapivirine vaginal ring and how they understood it to work to prevent HIV during the MTN-025/HOPE study through data collected from individual in-depth interviews. Ten women at each of the 6 HOPE research sites in Lilongwe, Malawi; Durban (2 sites) and Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe, were enrolled (n = 60). Despite its partial efficacy, women trusted the ring to prevent HIV even when condoms were not used. The action of the ring was understood by most, however, there were misunderstandings around how quickly or slowly protection was offered when the ring was inserted or removed. Counselling sessions adapted to address partial efficacy, a multi-layered HIV prevention plan and how study products work could alleviate inconsistent adherence and diminished protection and further support women in receiving the best protection from their HIV prevention product of choice.

Keywords Women · Dapivirine vaginal ring · Ring action · Efficacy · HIV prevention

Introduction

Women and adolescent girls have been the focus of HIV prevention clinical trials for many years because they account for about half of all new HIV acquisitions globally and 63% of all new HIV acquisitions in sub-Saharan Africa [1]. Due to many behavioural, social and structural factors women have historically faced challenges negotiating condom use with their male partners [2, 3]. Therefore, female-initiated prevention methods, including vaginal rings, have been in development to offer women a broader array of HIV prevention options. However, in order to make an impact on the HIV epidemic in sub-Saharan Africa [4], combination prevention options are ultimately required to address the different factors noted above, and to enhance protection with the use of partially efficacious products. It is for this reason that the continued development of HIV prevention products for women is imperative.

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The dapivirine vaginal ring was shown to be efficacious in two phase III studies – demonstrating reduced risk of HIV-1 acquisition by 27% in MTN 020/ASPIRE which was conducted from 2012 to 2015 [5] and by 31% in The Ring Study which was conducted from 2012 to 2016 [6]. This triggered two open-label extension studies which were implemented from 2016 to 2018 – MTN 025/HOPE [7] and IPM 032/DREAM [8]. On 24 July 2020, the European Medicines Agency (EMA) human medicines committee provided a positive scientific opinion about the ring to reduce the risk of HIV-1 acquisition among women aged 18 and older. In addition, the World Health Organization (WHO) recommended that the ring may be offered as an additional prevention choice for women at substantial risk of HIV acquisition as part of combination prevention approaches [9]. This expert opinion will help support the assessment of the dapivirine ring among regulatory authorities in sub-Saharan Africa as they move towards local approvals. More recently, the Medicines Control Authority of Zimbabwe (MCAZ) and the South African Health Products Regulatory Authority (SAHPRA) approved the use of the dapivirine ring in their respective countries [10, 11].

As part of understanding women's experience with ring use, the MTN-032 Assessment of ASPIRE and HOPE Adherence (AHA) sub-study was implemented in 2016 post-ASPIRE and in 2018 post-HOPE. AHA explored women's understanding of how the ring worked and its efficacy using qualitative interviewing methods with exited trial participants [12, 13].

A proven efficacious HIV prevention product may be accepted and favoured in that it provides an immediate health benefit in protecting against HIV. However, the scientific concept of efficacy, and how novel HIV prevention products biologically work can be complex and could impact study participants' product adherence and acceptability [14, 15]. In addition, misinterpretation of efficacy, especially in cases of a partially efficacious product, could lead to changes in social behaviour or the assumption that other HIV prevention options (e.g., condoms) are not needed negating the multi-layered HIV prevention approach resulting in the transmission of HIV [15, 16].

For this analysis, we explore women's interpretation of ring efficacy, knowing the ASPIRE study results of partial efficacy, and how they understood the ring to be acting within their body to prevent HIV. This information will help researchers understand how women view the ring as an HIV prevention option despite its partial efficacy, whether it was used in combination with other prevention methods or not and if knowing how the ring worked affected their ring use.

Methods

The HOPE study evaluated the safety of and adherence to the dapivirine ring with eligible HIV-uninfected ASPIRE participants being offered the active dapivirine ring to use for 12 months with a new ring being inserted monthly [7]. During HOPE, trained counsellors conducted HIV prevention options counseling sessions which were aimed at building a relationship with the participant to promote open communication about ring use, ring experiences and other HIV prevention options. During these sessions, counsellors gauged participants knowledge of the ASPIRE study results and provided further information on the rings efficacy as needed [17].

AHA enrolled former HOPE participants who agreed to be contacted for future studies. Potential participants were contacted in sequential order from a randomized list generated by the HOPE Statistical Center for HIV/AIDS Research and Prevention (SCHARP). Ten women at each of the six HOPE research sites in Lilongwe, Malawi; Durban (two sites) and Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe were invited to participate in an AHA screening/enrollment study visit 0–9 months after they had exited HOPE.

During the AHA study screening/enrollment visits, the informed consent form was administered to potential participants and eligibility criteria reviewed which included having participated in the HOPE study, able and willing to complete the required AHA study procedures and having study product dispensed to them during HOPE. Once participants were deemed eligible, the demographic and behavioural questionnaires were completed. Following this, in-depth interviews (IDIs) were conducted by trained female study staff in the language of the women's choice (English or local language) using a semi–structured interview guide. Women were informed that all information collected during the interviews was confidential and questions or concerns may be raised at any time. Discussions were facilitated around women's understanding of the ring efficacy in relation to the level of HIV protection they desired and how they thought the ring worked in their body to provide protection. These discussions included their thoughts on how quickly the ring offered protection after insertion and dissipated after removal, how well the ring protected against HIV, whether people required different amounts of drug to be protected and what affected the amount of drug in one person's body compared to another person.

IDIs were audio-recorded, transcribed, and translated into English (if conducted in a local language). Quality control checks were conducted with local site staff including comprehension of local terminology. Transcripts were thereafter uploaded to Dedoose (Version 8.1.8), a qualitative

software programme, for coding. Coding allowed the raw contextual data to be summarized and condensed with its meaning extracted. Analysts, including the lead author, used an iteratively developed codebook to descriptively code for key themes and topics. Intercoder consistency was confirmed at a level above a mean kappa score of 0.70 for 10% of transcripts across five coders and code application queries were discussed and resolved with the coding team. Data assigned with the parent code "ring" and related subcodes, "efficacy", "mechanism of action", "side effects", and parent code "seroconversion" were analyzed. Selection and interpretation of results were discussed with co-authors representing three of the research sites to ensure correct presentation of findings across settings.

The AHA study protocol was approved by the Institutional Review Boards at RTI International, and at each study site and regulated by the U.S. National Institutes of Health and the Microbicide Trials Network.

Results

Study sample

Eighty-five women were screened and sixty of these women were enrolled into AHA. Twenty-five women were not enrolled due to the eligibility criteria not being met (early termination from HOPE and refusal to be contacted for future studies), unavailability, disinterest, relocation and incomplete screening. Two women were not included in the analysis due to inappropriate enrolment, resulting in an analytic sample of n = 58. Detailed characteristics of the study sample have been presented previously [12]. Women averaged 32 years of age (range 23–48), with 44.8% being married, and 84.5% having the same partner since exiting HOPE.

Efficacy

Several women understood that the ring could prevent them from acquiring HIV if used correctly and consistently and that there would be less or no protection if not used or used inconsistently. Now that HOPE had ended and they no longer had access to the ring, many women mentioned that they felt concerned that they were now unable to protect themselves from HIV.

> *"I feel sad knowing that I am no longer using the ring because now I know that I am not protected at all so that makes me feel sad especially knowing that there is something that I could be faced with at any time while I am not protected. I can easily get the infection* [HIV]*."* (Johannesburg, South Africa).

Among the women that felt that the ring protected them, some understood the partial efficacy whilst others reported varying levels of efficacy, even up to 100%.

> *"So far, I put it at 75%* [referring to the protection the ring offers] *.... Because we do not know yet if it's protecting effectively. It protects, but I wouldn't know if it does so up to 100%. It has its limits, that it works to such and such a level. That's how much it is able to protect*." (Chitungwiza, Zimbabwe).

A few women openly discussed having sex with a primary or casual partner living with HIV but continuing to test negative for HIV, which further confirmed to them that the ring provided protection.

> *"Another thing is that when you wear the ring, even if you have sex with someone who has HIV, you will not contract it because the ring is medicated."* (Lilongwe, Malawi).

Others felt so protected by the ring that even when condoms were not used with a partner or multiple partners that they distrusted, they felt confident that they were still protected.

> *"What excited me about the ring is that with the life of nowadays, you cannot trust your partner because what he does wherever he goes, you never know but the ring addressed any worries because I knew I was protected."* (Lilongwe, Malawi).

A woman from Durban, South Africa, reported that she knew of women who seroconverted after the ASPIRE study ended and before the HOPE study began and the reason for this was that these women did not have access to the ring during this period to protect themselves. Similarly, a woman from the second Durban site mentioned that she knew of women who removed the ring and seroconverted during HOPE, while those that used the ring consistently did not acquire HIV.

> *"Because there isn't anyone who I know who uses the ring and says they have been infected.... The people who got infected were the people who used to take the ring out."* (Durban, South Africa).

Another woman who seroconverted during study participation in HOPE, openly discussed not using the ring during

the HOPE study and being upset with herself for not using the protection that was available to her.

> *"I am annoyed by the way I was using the ring, which led to me to not being protected and eventually ended up getting infected with the virus, whilst I was provided with a chance to protect myself."* (Durban, South Africa).

A misperception that the ring could be efficacious towards other non-HIV viruses was implied by one woman from Lilongwe, Malawi, who explained that the ring may have protected her from malaria and influenza as she did not have these illnesses when she used the ring however once she removed it, she contracted malaria and influenza.

> *"I don't know what connection was there between the ring and my body because I was not feeling unwell; I was not having malaria. I had healthy life but after I had removed the ring, it happens that I do have malaria, flu and the like; illnesses but when I was using the ring I did not have these illnesses."* (Lilongwe, Malawi).

Method of action

Most women demonstrated having an adequate understanding of how the ring worked– in HOPE each ring had the same amount of dapivirine, a new ring was inserted monthly, drug was released from the ring and entered the body/bloodstream to provide protection against HIV - information they gained from counselling and education sessions during their participation in ASPIRE and HOPE. Dapivirine blocking the contact points in the body from where a woman gets HIV and vaginal secretions released during sex mixing with dapivirine and then destroying the virus were the other ways women mentioned they thought the ring worked in their body.

> *"When you insert the ring in your body it releases the Dapivirine into your system…. and blocks all the contact points you can contract HIV from. It blocks all those points and keeps you protected for that period."* (Johannesburg, South Africa).

A few women also mentioned that sex workers and women that engage in numerous sex acts daily with different men would need more dapivirine to be protected, suggesting a perception that the amount of dapvirine one needs depends on the number of sex acts they engage in or on the number of men they sexually engage with.

> *"But in the case of these other women* [sex workers] *they would need quite a lot of the drug just because if she has sex with such people on a daily l basis, what would happen to her?"* (Chitungwiza, Zimbabwe).
> *"Perhaps one has too much sex and another does not. That's what I think…. do you know there are people who have sex with seven or eight people per day? In my view, it is better for the level to be high than to be low."* (Chitungwiza, Zimbabwe).

A couple of women compared the action of the ring to their understanding of the contraceptive injection that is reported to not work immediately following administration. In addition, many women had different thoughts on how quickly the ring provided protection once inserted, ranging from immediately to hours, days or months. Similar ranges were reported by women for when they thought the ring stopped providing protection once removed.

> *"Medication from the ring in my body will be higher, so it will take longer for it to be completely out my body. It won't be the same as when it is entering my body, because when it's entering my body it takes long since the body hadn't adapted to it. Maybe 3 or 4 months when it's coming out* [protection offered for 3 or 4 months after removal] *but when it's entering the body I think it takes a month* [protection provided after one month on insertion], *that is what I observed*." (Durban, South Africa).

Some women reported perceptions that dapivirine was being removed from the ring when the ring was removed and washed, which in turn affected the amount of drug to be released into the body when the ring was reinserted.

> *"If you wash it, I think you would be washing off the medicine. I think that is what they meant that if you wash it then in a way you are washing off the medicine which reduces it."* (Kampala, Uganda).

Other contributing factors that were seen by participants to affect the release of the drug in the body included the use of other medications, different blood types, different body types, stress or hormonal levels, not enough blood in the body for the drug to circulate and lifestyle decisions like exercise, alcohol intake or eating unhealthily.

> *"I think your lifestyle if you exercise and you eat healthy and all those things maybe the drug would be like more effective in your body. Then if you have a very unhealthy lifestyle, you drink a lot, you don't drink enough water, I am just thinking it may affect the*

level of drug use in your body…. So, if you are having a healthy lifestyle, I think it's a correct environment for your drug to work perfectly in your body." (Johannesburg, South Africa).

One woman hypothesized that the type of a person's flesh might be a factor affecting the release of the drug. She explains that if one's flesh is tough like a "hard Mashona" (local breed of cattle), their bodies will resist the drug.

"But you can see that the person is striving and same applies to you. Perhaps we are even striving in a similar way, but at the end you find the other has more drug, and yours is lower. So, I sometimes think it's the type of flesh that resists. I'm not quite sure. There is flesh the tough type such as the 'hard Mashona' type [term used to refer to local breed of cattle whose flesh is tough]. *So, I think that type resist the absorption of a lot of the drug."* (Chitungwiza, Zimbabwe).

Another woman described how she remained HIV negative through ASPIRE when she used the placebo ring. However, during HOPE when she used the active ring, she seroconverted. She believed that the dapivirine in the ring revealed the virus which had been hidden in her body through the ASPIRE trial. She went on to say that she was glad she used the ring even though she seroconverted because if dapivirine did not release the virus, she would still think she was HIV negative.

"In my view, when I started using the ring, the drug is the one which caused the virus to be exposed. When I was tested previously, I had been using a ring which had no drug. In my opinion maybe the power of this drug exposed the virus… I'm happy about the ring because, eh if I had not used the ring, I could probably still be thinking I'm HIV negative." (Chitungwiza, Zimbabwe).

Discussion

The data in this analysis are suggestive of two key findings. First, the interpretation of the partial efficacy of the ring was varied among the women with some women depending solely on the ring to offer full protection against HIV in the absence of other prevention methods. Second, there were some misconceptions among women of how the ring worked in the body, how drug was released or removed from the ring and when the ring offered protection after insertion and dissipated after removal. In-depth qualitative understanding of how end-users comprehend efficacy, partial efficacy and biological mechanisms of use offer essential information to maximize the public health impact of an intervention, and commensurate human safety.

Some women interpreted the efficacy of the ring differently from the ASPIRE study results that were provided to them [5]. ASPIRE reported the ring to be 27% effective [5], and some of the AHA study participants thought that the ring offered more protection than this, perhaps to provide them with some peace of mind when condoms were not used. Additionally, women felt less able to protect themselves from HIV once the HOPE study was completed as they did not have the ring to use for protection. Oral pre-exposure prophylaxis (PrEP) can also be used discretely and its use controlled by women, however, this HIV prevention method was not mentioned as an option whereas condoms were mentioned frequently. The daily pill burden, accessibility constraints in many settings and associated stigma of oral PrEP being an antiretroviral still affect its popularity, adherence and uptake [18, 19]. Perhaps for these research participants, the ring was seen as the only efficacious HIV prevention product they had easy access to, and that they could control and use covertly.

Women who demonstrated understanding of partial efficacy feared being at risk for HIV but still felt confident and comfortable that they had some level of protection provided by the ring. Discussions around seroconversion occurring when women did not have access to the ring between ASPIRE and HOPE or non-adherence during HOPE study participation further reiterated a strong belief that the ring protected them from HIV acquisition.

Women further emphasized their trust in the efficacy of the ring when they still felt protected during condomless sex with multiple partners or partners living with HIV lending to the theory of whether HIV prevention options lead to increased HIV risk through risk compensation [20–23]. Regardless of social behaviour which is deeply rooted in structural, cultural and community contexts, women need to understand the efficacy of different HIV prevention products available to them and be able fit it into their lives and lifestyles successfully. More importantly, women should be able to make an autonomous decision on the best HIV prevention product that works for them.

Researchers in HIV clinical trials and health care workers in HIV prevention programs should look at ways of developing counselling and education to improve women's understanding of the efficacy of HIV prevention products and how to choose the best tools for their health goals. These messages could be communicated through a robust package of sexual and reproductive health (SRH) services which covers sexually transmitted infection (STI) management,

family planning services, PrEP awareness and access, and the need for combination prevention [4, 24].

Most women understood how the rings works to prevent HIV, but not all. Including information about how the ring works in the body in future ring demonstration projects can provide an added benefit to proactively address and mitigate misconceptions about its method of action. Counselling messages could address such misconceptions like protection being offered months after the ring is removed, dapivirine causing HIV to be revealed in a person's body and release of the drug being affected by external or physiological factors. Additionally, comprehension of study designs, research goals and how study products work among male partners could aid in promoting male partner support to women participating in HIV prevention trials [25].

Women had varying thoughts on the timeline for when the ring offered protection once inserted and stopped providing protection once removed. This could have led to poor adherence, such as inserting the ring just before sex with the belief that the ring offers immediate protection on insertion. Counselling and guidelines for future marketing of the ring should focus on keeping the ring inserted daily for a full month, as well as the period needed for the ring to be used (inserted and removed) to offer an appropriate level of protection.

There are limitations to this research that should be taken into consideration. The data collected is from a randomly selected sub-set of women from HOPE and therefore may not be reflective of the full cohort of HOPE study participants. The interviews were conducted after women exited the HOPE study and therefore responses may be subject to recall bias.

Even though the dapivirine ring was proven to be partially efficacious, some women trusted it to prevent HIV acquisition even when condoms were not used. Partial efficacy must be emphasized during education on the ring and how it works within a multi-layered HIV prevention plan. Women should be supported in deciding how they can best incorporate ring use into their lives to get the best protection. The action of the ring was understood by most however some misunderstandings around how quickly or slowly protection is offered when the ring is inserted or removed needs to be addressed as this can lead to inconsistent adherence and diminished protection. Counselling sessions should be adapted to speak to how study products work in the body which may enhance comprehension and positively impact overall HIV prevention research goals.

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Author contributions Kalendri Naidoo was involved in the study implementation at the study site, data collection, data interpretation, data coding and analysis and writing this article. Elizabeth T. Montgomery was involved in the study design, overall study implementation, data interpretation and article review. Sarita Naidoo was involved in the study design, overall study implementation and article review. Ariana W.K. Katz was involved in the study design, oversaw study implementation, data coding and analysis, data interpretation and article review. Morgan Garcia and Lydia Soto-Torres were involved with overall study implementation and article review. Leila E. Mansoor and Krishnaveni Reddy were involved with study implementation at the study site, data collection and article review.

Data availability The data will not be available to the public. If an individual is interested in exploring the data, they should contact the lead author.

Code availability N/A.

Declarations

Conflicts of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Ethics approval The MTN 032 study protocol was approved by the Institutional Review Boards at RTI International, and at each study site and regulated by the U.S. National Institutes of Health and the Microbicide Trials Network.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All participants were informed that any publication of this study will not use their name or identify them personal.

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CHAPTER FIVE

Paper 3:

Title: Qualitative Perceptions of dapivirine VR adherence and drug level feedback following an open-label extension trial.

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Qualitative Perceptions of Dapivirine VR Adherence and Drug Level Feedback Following an Open-Label Extension Trial

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Background: There continues to be a need for HIV prevention options that women can initiate and use autonomously. The dapivirine vaginal ring (VR) has been shown to have a favorable safety profile and reduce the risk of HIV-1 acquisition. We report on women's experiences with VR adherence during the MTN-025/HIV Open-label Prevention Extension (HOPE) study and responses to Residual Drug Level (RDL) results.

Setting: Ten women at each of the 6 HOPE research sites in Lilongwe, Malawi; Durban (2 sites) and Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe, were randomly selected (n = 60).

Methods: After confirmation of eligibility criteria, in-depth interviews were conducted where available RDL results were presented.

Results: Many women with low RDL release measurements deflected blame onto other factors (the ring, the drug, and faulty testing machines) and distrust of the testing method. The disclosure of RDL results enabled some users to discuss their challenges experienced (fear of partner objections, perceived side effects, and removals during menses). Consistent users reported important motivators (support from others, protection from HIV, and enhanced sexual experiences from the VR).

Conclusion: The VR provided a sense of security for some women; however, adherence was still challenging for others regardless of it being a female controlled, long-acting HIV prevention technology. Adherence measurements may not be sustainable in the real-world implementation of the VR, although they can be seen as a benefit as they provide a better understanding of actual product use and provide women with a platform to discuss their experiences.

Key Words: women, adherence, dapivirine vaginal ring, qualitative research, sub-Saharan Africa, residual drug levels

(*J Acquir Immune Defic Syndr* 2021;86:e90–e96)

INTRODUCTION

Women in sub-Saharan Africa are disproportionately at risk for HIV compared with men in the same region and women in other parts of the world.[1] Although condoms are effective in preventing HIV transmission during sexual intercourse, many women find it difficult to negotiate their use with male partners because of many behavioral, social, and structural factors.[2] When taken as indicated, oral pre-exposure prophylaxis (PrEP)

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is a safe and effective HIV prevention method for both men and women; however, the uptake and consistent use of the daily dosing regimen has been challenging for women in clinical trials[3,4] and demonstration projects.[5]

Studies have shown that adherence to HIV prevention technologies has been challenging for women. The FEM-PREP team attributed poor adherence to low HIV-risk perception and difficulty taking daily oral pills.[4] In VOICE-C,[6] a qualitative substudy after the VOICE trial of vaginal gel and oral tablets for HIV prevention, women reported that unknown efficacy, distrust of researchers, dangers of research participation, and an association of antiretroviral's with illness led to poor adherence. In VOICE-D,[7] another qualitative substudy of VOICE, poor adherence was reported because of a variety of reasons such as mistrust of the research, community rumors, burdens of a daily regimen, unpleasant experience using products, unknown efficacy, busy lifestyles, unsupportive partners, side effects, and nonuse during menses. Consequently, there continues to be a need for HIV prevention options that women can initiate, use autonomously, and which mitigate daily adherence challenges.

Two recently completed Phase 3 trials, the Microbicide Trials Network (MTN)-020/A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) and International Partnership for Microbicides-027 (The Ring Study) showed the dapivirine vaginal ring (VR) (Fig. 1) to be well tolerated and reduce the risk of HIV-1 infection by 27% and 31%, respectively, when used as indicated.[8,9] The dapivirine VR, an investigational new drug, is an off-white flexible ring containing 25 mg of dapivirine and when inserted, provides sustained release of dapivirine for a minimum of 1 month.[8,9]

FIGURE 1. Dapivirine VR.

The dapivirine VR was subsequently tested for safety and adherence in multisite, open-label extension, phase III studies–MTN-025/HIV Open-label Prevention Extension (HOPE) and International Partnership for Microbicides-032/Dapivirine Ring Access and Monitoring (DREAM).[10,11] Used VRs were collected and tested for residual drug levels (RDLs) (ie, the amount of dapivirine that remained in the VR, which provided an estimation of the amount of drug that was released). Overall, 90% of used VRs in HOPE and 95% of used VRs in DREAM indicated at least some use–not necessarily consistent use.[10,11] The European Medicine Agency recently adopted a positive scientific opinion about the ring for use among women aged 18 and older to reduce the risk of HIV-1 infection. This is an important step toward regulatory approvals in African countries and will be the first female controlled, long-acting HIV prevention technology available.

As part of understanding sociocontextual and trial specific issues that impacted VR adherence, the MTN-032 Assessment of ASPIRE and HOPE Adherence (AHA) exploratory substudy was implemented. This is one of the first studies to report on women's experiences of dapivirine VR adherence and their responses to RDL results in the context of an open-label extension trial. Findings from this analysis can be used to inform strategies for women using the VR postlicensure.

METHODS

The MTN 025 (HOPE) study evaluated the safety of and adherence to the dapivirine VR.[10] Eligible HIV-uninfected ASPIRE participants were offered the active dapivirine VR that was replaced monthly over 12 months. Study follow-up visits occurred monthly for the first 3 months and quarterly thereafter to allow for a more real-world type of setting such as oral PrEP. Women could decline the VR and still enroll into the study and accept the VR at any point if they changed their mind. During the HOPE study, HIV prevention options counseling sessions occurred at enrollment, follow-up months 1, 2, 3, 6, and 9, and at the Product Use End Visit. Sessions were conducted by certified counselors and were designed to be a collaborative open conversation between counselor and participant. Counseling sessions centered around choice to use the VR or other HIV prevention strategies, RDL result provision, accurate reporting of VR use, and the participants experience with her HIV preventative method of choice. Counseling also included messages that RDL testing might not be 100% accurate because of the variability in the tests and emphasized the importance of the participant's reported experience.

The data presented here constitute women's ring use perceptions and experiences, captured through in-depth interviews (IDIs) conducted during the AHA study. AHA occurred 0–9 months after women exited from HOPE and included provision of all their available RDL results, categorized from 0 (no drug release) to 3 (high rate of drug release) using the Residual Drug Feedback Over Time Tool (Fig. 2).

Women who received study product and provided permission to be contacted for future studies in HOPE were eligible to participate in AHA. Women were contacted in a sequential order from a randomized list generated by the HOPE

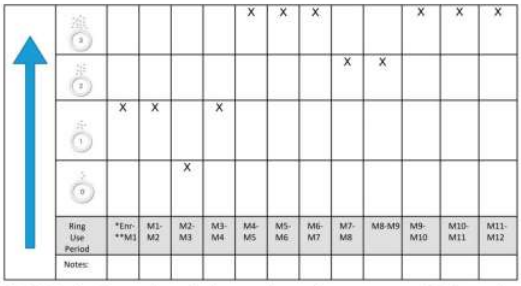

FIGURE 2. Example of the tool used to capture RDL results. *Enrolment. **Month.

Data Management Centre. Ten women at each of 6 HOPE research sites in Lilongwe, Malawi; Durban (2 sites) and Johannesburg, South Africa; Kampala, Uganda; and Chitungwiza, Zimbabwe, were randomly selected to participate in IDIs. Recruitment was stratified in a 1:3:1 ratio (low: middle: high release) according to the dapivirine RDL from the Month 1 VR to ensure a diversity of adherence perspectives.

After confirmation of eligibility criteria, informed consent and demographic and behavioral questionnaires were administered by trained study staff. IDIs were then conducted in the language of the women's choice (English or local language) using a semistructured interview guide. Women were reminded that the interview was about their experience during HOPE, it was confidential and questions/concerns could be raised at any time. Thereafter, they were shown their available RDL results using the same tool that was presented to them during HOPE (Fig. 2). A discussion was then facilitated on how they felt about the results, including if they believed the RDLs matched their actual use and views on the RDL testing method, barriers (RDL results of 0/1), and motivators (RDL results of 2/3) to ring use.

IDIs were audiorecorded, transcribed, and translated into English (if conducted in a local language) with quality control checks. Transcripts were then uploaded to Dedoose (Version 8.1.8), a qualitative software program, for coding. Analysts, including the lead author, used a codebook developed iteratively and descriptively coded for key themes and topics. Intercoder consistency was confirmed at a level above a mean kappa score of 0.70 for 10% of transcripts across 5 coders, and code application queries were discussed and resolved with the coding team. Data assigned with the parent code "adherence" and related subcodes were stratified by average RDL results and compiled into summary memos.

For the purpose of this analysis alone (not presented to the women), average RDL results were calculated by summing the total monthly RDL scores and dividing by the number of months of use. Participants were then categorized as follows: low rate of release = an average rating of between 0 and 1, middle rate of release = an average rating of >1 to <2, and high rate of release = an average rating of between 2 and 3. Quantitative data were tabulated using Stata 15.0 (Statacorp, College Station, TX).

The AHA study protocol was approved by the Institutional Review Boards at RTI International and at each study site and regulated by the U.S. National Institutes of Health and the MTN.

RESULTS

Study Sample

Eighty-five women were screened, and 60 of these women were enrolled into AHA. Two women were not included in the analysis because of inappropriate enrolment, resulting in an analytic sample of n = 58. Thirteen women refused screening/enrolment citing reasons of unavailability (n = 10) and disinterest (n = 3).

Detailed characteristics of the study sample are presented by average RDL results in Table 1. Women averaged 32 years of age (range 23–48), with less than half (44.8%) married, and 84.5% reported having the same partner since exiting HOPE. More than half (57.1%) reported that their primary partners were HIV-negative, although many (41.1%) did not know their partner's HIV status, or whether their partners had other sex partners (66.1%). All women, except for one, (98.2%) said that they would use a VR in future, with 74.5% being worried about acquiring HIV in the next 12 months.

The average RDL results indicated that 20.6% (n = 12) of women were in the low rate of release category, 41.3% (n = 24) were in the middle rate of release category, and 37.9% (n = 22) were in the high rate of release category. Approximately two-thirds of the women, (n = 37; 63.7%), had all 12 months of RDL results to review. Those with less than 12 months of RDL exited early from the study, ring use was discontinued by study staff (eg, seroconversion, pregnancy) or had chosen not to use the VR.

In Agreement With RDL Results

There was generally more agreement about how well the RDL results matched behavior among women in the high RDL category compared with the low/middle RDL categories. Furthermore, those who felt that their RDLs matched VR use (n = 19/58; 32.8%) predominantly trusted the RDL testing method (n = 18/19; 94.7%) (Table 2).

Women in all 3 RDL categories reported that support from partners, other women and study staff (counseling and engagement activities) helped them to sustain adherence to VR use. Women who faced adherence challenges mentioned that even if they had low RDL results, study staff were still encouraging during the counseling sessions by reassuring women to continue using the VR consistently.

"The staff asked us 'please use the ring at all times,' 'it helps' *and* 'the good thing was that you had a choice, it was up to you to choose to use the ring or not'….. *It did encourage me….."* (Durban (1), South Africa, RDL Category: Low)

Protection from HIV was a key motivator for VR use among the women in all 3 RDL categories, across all sites. Women in the middle and high categories who felt that they were at a high risk for HIV because of distrust of their male

TABLE 1. Women's Characteristics Presented by Average RDL Release Results

		Average of Month 1–Month 12 RDL Results		
	All Sites (n = 58)*	Low = 0–1 (n = 12)	Middle = >1–<2 (n = 24)	High = 2–3 (n = 2
Site				
Johannesburg, South Africa	9 (15.5%)	1 (8.3%)	3 (12.5%)	5 (22.7%)
Durban (1), South Africa	10 (17.2%)	3 (25.0%)	6 (25.0%)	1 (4.5%)
Durban (2), South Africa	10 (17.2%)	4 (33.3%)	1 (4.2%)	5 (22.7%)
Kampala, Uganda	10 (17.2%)	3 (25.0%)	4 (16.7%)	3 (13.6%)
Chitungwiza, Zimbabwe	10 (17.2%)	1 (8.3%)	4 (16.7%)	5 (22.7%)
Lilongwe, Malawi	9 (15.5%)	0 (0.0%)	6 (25.0%)	3 (13.6%)
Age–mean (median, min–max)	31.8 (30.0, 23.0–48.0)	28.6 (27.5, 23.0–37.0)	31.8 (31.5, 23.0–45.0)	33.5 (30.5, 25.0–48.
Highest level of education				
Primary school, not complete	8 (13.8%)	2 (16.7%)	2 (8.3%)	4 (18.2%)
Primary school complete	19 (32.8%)	4 (33.3%)	9 (37.5%)	6 (27.3%)
Secondary school complete	24 (41.4%)	3 (25.0%)	11 (45.8%)	10 (45.5%)
College/university complete	7 (12.1%)	3 (25.0%)	2 (8.3%)	2 (9.1%)
Earn income				
Formal employment	19 (32.8%)	5 (41.7%)	9 (37.5%)	5 (22.7%)
Self-employed	16 (27.6%)	4 (33.3%)	5 (20.8%)	7 (31.8%)
Others (eg. social welfare)	8 (13.8%)	2 (16.7%)	4 (16.7%)	2 (9.1%)
Relationship status				
Currently married	26 (44.8%)	4 (33.3%)	11 (45.8%)	11 (50.0%)
Has a primary sex partner	56 (96.6%)	12 (100.0%)	23 (95.8%)	21 (95.5%)
Same partner from HOPE	49 (84.5%)	10 (83.3%)	21 (87.5%)	18 (81.8%)
Primary partner has other sex partners*				
Yes	11 (19.6%)	2 (16.7%)	7 (30.4%)	2 (9.5%)
Unknown	37 (66.1%)	7 (58.3%)	15 (65.2%)	15 (71.4%)
Primary partners HIV status*				
HIV positive	1 (1.8%)	1 (8.3%)	0 (0.0%)	0 (0.0%)
HIV negative	32 (57.1%)	6 (50.0%)	14 (60.9%)	12 (57.1%)
Unknown	23 (41.1%)	5 (41.7%)	9 (39.1%)	9 (42.9%)
Worried about getting HIV in the next 12 months*				
Not worried at all	14 (25.5%)	2 (20.0%)	6 (25.0%)	6 (28.6%)
A little/somewhat worried	21 (38.2%)	4 (40.0%)	11 (45.8%)	6 (28.6%)
Very/extremely worried	20 (36.4%)	4 (40.0%)	7 (29.2%)	9 (42.9%)
Would use a VR in future*				
Yes	54 (98.2%)	10 (100.0%)	24 (100.0%)	20 (95.2%)
Unknown	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (4.8%)

*Responses missing in some categories.

partners were motivated to use the VR, knowing that it reduced HIV risk and wanting to remain HIV negative.

"I wanted to be protected because sometimes you cannot trust your partner since you never know what he does when he goes out. That was why I was motivated to use the ring consistently." (Lilongwe, Malawi, RDL Category: Middle)

A woman from Durban, South Africa, explained that women were more motivated to use the VR consistently in HOPE as compared with ASPIRE. This behavior was attributed both to taking the study more seriously because the VR was now shown to be well-tolerated and reduce HIV risk, and being able to have the opportunity to use the VR since their peers from ASPIRE could not join HOPE because of seroconversion post-ASPIRE.

"Everybody was willing to use it now …… maybe everyone's eyes started to open and they started to take this whole thing seriously…… the seriousness of the matter and the fact that they know people who were in ASPIRE who were not able to come back to HOPE because along the way they found they had become HIV positive" (Durban (1), South Africa, RDL Category: Middle)

Another motivating factor reported from the middle and high RDL categories was that the VR increased sexual pleasure for male partners. Some women reported that their male partners felt that the VR made their vaginas "tighter," whereas other women mentioned that male partners just enjoyed sex more when they knew that the VR was inserted.

"At the beginning he (partner) *said, 'Ah, it appears the ring causes sex to be more enjoyable, because it's all different*

TABLE 2. Trusting/Not Trusting the Method Used to Test the VR vs. Residual Drug Level Results Matching/Not Matching How the Woman Used the VR

	Residual Drug Level (RDL) Match/Do not Match How the Woman Says She Used the VR		
Trust/Does not Trust the Method Used to Test the VR	**RDL Matched Ring Use** N (%)	**RDL did not Match Ring Use** N (%)	**Total** N (%)
Trusts the method	18 (94.7)	15 (38.5)	33 (56.9)
Does not trust the method	1 (5.3)	24 (61.5)	25 (43.1)
Total (%)	19 (32.8)	39 (67.2)	58 (100.00)

now.' …… He actually encouraged me saying, 'Insert your ring.' *So, I kept the ring inserted."* (Chitungwiza, Zimbabwe, RDL Category: High)

Many women with inconsistent RDL results openly discussed challenges in using the VR. The most common reported reason across all sites and RDL categories (more common in the low RDL category) were actual or perceived objections to the VR by male partners. Women described how they removed the VR before seeing their partners or when their partners told them to remove it although they knew they should not remove it, to avoid any arguments or violence within the relationship.

"…… when you are married to somebody there are instances where you conform to his wishes even though you might have your own desires…... So, the moment he said, "Remove the ring," *I would remove it. Even though I had my own thoughts and views, there were times he would override that."* (Chitungwiza, Zimbabwe, RDL Category: Low)

Some women in the high RDL category told their partners that they had removed the VR when it was still in place, and these partners believed this because they did not feel it during sex.

Negative experiences interpreted as side effects from VR use were mentioned across all RDL categories resulting in VR removals. Reported symptoms included headaches, dizziness, increased vaginal wetness, widening of the vagina, abdominal and pelvic pain, vaginal discharge, odor, or itching. Some of these women accepted that the VR was not causing these perceived "side effects" after counseling from study staff or self-realization when the "side effect" continued after removing the VR. Some women in all RDL categories reported removing the VR for the duration of menses or for a short time during menses to wash and reinsert it because they believed it was unhygienic not to wash the menstrual blood from the VR.

Disagreement With RDL Results

Most women (n = 39; 67.2%), predominantly in the low and middle RDL categories, felt that their RDLs did not match their actual VR use (Table 2). Of the 39 women, 24 (61.5%) indicated that they distrusted the RDL testing method (Table 2). Women in the low and middle categories sometimes explicitly referenced the reason that the RDL results may not be 100% accurate.

Some women who reported that the RDLs were inaccurate did not describe periods of nonuse. Instead, they provided several different explanations for this discrepancy between RDLs and perceived adherence to the VR. These included external factors (eg, condoms or traditional medications affecting the release of dapivirine), biomedical factors (eg, the body being resistant to drug uptake during periods of stress, VR contact with semen and sex itself prevented drug release, washing the VR removed some of the drug, or different blood types affecting the release of dapivirine), and technical factors (eg, delays in inserting a new VR monthly and not inserting the VR correctly contributed to the amount of dapivirine being released or the VR having the incorrect amount of drug before insertion). A small number of women believed that the RDL testing machines were defective.

These are examples of women who described how their blood type and stress played a role in low RDL results:

"*Some blood types quickly absorb some things. This implies that when I insert the ring and the drug coming from the ring is compatible with my blood, the drug quickly saturates my body"* (Chitungwiza, Zimbabwe, RDL Category: Middle).

"I kept the ring inside inserted, …… during June when I was writing exams I was stressed, maybe my stress level or my hormonal levels affected the ring drug use in my body, so maybe that affected it….." (Johannesburg, South Africa, RDL Category: Middle).

Some of their narratives suggested they felt confused about the low RDL results because they believed they had used the VR consistently and as instructed by the research team.

"……*but when I would receive the results that were not true, I would be hurt, because I would not understand how? …… because I used to use the ring all the time, which meant it was always in my blood. That is where I would get confused*" (Durban (1), South Africa, RDL Category: Middle)

DISCUSSION

The data in this analysis are suggestive of 3 key findings about women's use of the dapivirine VR during an open-label extension trial. First, many with low release measurements reported good adherence, and cited other factors as rationale for low RDLs, including the testing method. Second, the disclosure of RDL results enabled some users to discuss their challenges experienced with VR use. Third, consistent users reported important motivators to VR use.

Many women with low RDL results voiced their distrust of the testing method, a finding similar to VOICE-

D where women attributed nondetection of the drug to problems with the pharmacokinetic testing.[7] It should be recognized that RDL testing on returned VRs provided an estimate of VR use and was not 100% accurate because of the variability in the tests. It was therefore possible for a woman to receive results that were not reflective of her actual use. Counseling flipcharts contained a message that results "may not be 100% accurate," which may have led women toward distrust of the testing method–irrespective of their actual use. Future studies with PK testing should carefully consider how these messages might be received, interpreted, and adjusted.

Some women with actual low use may have been uncomfortable admitting to nonadherence, and therefore cited the VR, the drug, defective testing machines and distrust of the testing method as reasons for the low RDLs. These factors may have been named to avoid conflict or judgment by study staff and to present themselves in a way that they believed would be viewed favorably by study staff. Although there were some admissions of nonuse in AHA, most likely facilitated by the RDL results disclosure, women still sought to provide socially desirable explanations.

These findings are again similar to those from the VOICE substudies, where women reported themselves to be perfect adherers with contradicting pharmacokinetic results. Women cited multiple reasons for misreporting adherence, including human nature, self-presentation to study staff, fear of repercussions (study termination and experience of HIV-related stigma), and avoiding inconvenient additional counseling.[12,13]

During phase one of the AHA study, post-ASPIRE, women's reported reasons for nonadherence were similar to this post-HOPE cohort, including removals during menses,[14,15] perceived side effects from VR use and fear of or actual partner opposition to the VR.[16]

The consistency of the results across studies strengthens the reliability of our findings and demonstrates that African women in these settings have had adherence challenges during research trials irrespective of the type of study product, mode of administration or its efficacy. Many of these challenges are rooted in structural factors related to inequitable gender norms, HIV-related stigma, risk perception, and research suspicion–all of which require broader intervention approaches than biomedical technologies. In addition, it seems that in some cases, women feel their level of adherence is adequate and acceptable given their life circumstances.[16] Some barriers, such as removals because of menses and perceived side effects can be preempted in future marketing of the VR through health information and counseling.

Women felt conflicted regarding removing the VR for fear of their partner feeling it during sex versus keeping the VR inserted to have some protection against HIV which alludes to the gender power inequalities still experienced in relationships and the need for a discreet HIV prevention technology. In this study, we measured men's experiences with the VR in FGDs which will be presented elsewhere.[17] Counseling and guidelines for VR rollout should speak to the level of protection offered with intermittent use. An important future research question will be to determine the level of protection offered if the VR is removed for sex.

The 3 main reasons women offered for their consistent VR adherence during HOPE was support from others (partners, fellow women/friends, and study staff), confidence in the VR providing protection from HIV and the VR enhancing sexual experiences, which is consistent with previous qualitative research findings among women who participated in ASPIRE.[18] Using the VR seemed to give women a sense of security, when they were unsure of their partners' fidelity and risk-related behavior which reiterates the need for women to have access to a female controlled HIV prevention technology. This was confirmed in a qualitative study among women in ASPIRE where 9 product formulations were presented to gauge preference— women preferred the long-acting products (rings, implants, and injections) for its protection, ease of use, discreetness, and less frequent dosing.[19] It may be useful to incorporate this into future marketing communications of the VR.

There are limitations to this research that should be taken into consideration. The data collected are only from a subset of women from HOPE, randomly selected based on their Month 1 adherence (low, middle, and high release) using a 1:3:1 ratio and therefore may not fully reflect the ring-use experiences of all women participating in HOPE. Furthermore, the interviews were conducted 0–9 months after women exited the HOPE study, so recall bias must be considered when interpreting the data.

Although women chose to join the HOPE study and had the opportunity to decline the VR, adherence was still a challenge for some women regardless of it being a female-controlled, long-acting HIV prevention technology. This suggests that women may have joined for other reasons such as health benefits provided during participation; alternatively, they may have joined with an intention to use the VR but then faced challenges that led to non or intermittent adherence. Women need a diverse set of discreet options that can be incorporated in their lives depending on their immediate or long-term needs, situation, and lifestyle. Adherence measurements may not be sustainable in the real-world implementation of the VR; however, they can be seen as a benefit as they provide a better understanding of actual product use and provide women with a platform to discuss their experiences. In addition, understanding a woman's reported use beyond RDL results provides insight into how the VR is understood to work and is incorporated into women's lives. As in the trial setting, person-centered adherence counseling to identify and address misunderstandings and challenges will facilitate successful real-world implementation of the VR.

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CHAPTER SIX

6. General Discussion

6.1 Summary of Findings

The findings of this thesis provided interesting information on the views of women participating in an HIV OLE study.

The motivations women cited for joining the OLE study included access to good healthcare, protection against HIV, financial reimbursement and the need to find an HIV prevention method were most commonly reported similar to the findings of previous research about why participants chose to join HIV prevention clinical trials (1, 2, 3). Regardless of the study design, the benefits offered from clinical trials (prior to efficacy determination) versus OLE studies (following efficacy determination) seemed to be viewed equally by participants. Although many OLE participants worried that their male partners might expose them to HIV, they chose to remain in their relationships and avoid conflict or confrontation with their partners by discreetly using the ring to protect themselves. Researchers and public health practitioners should better understand the social and personal motivators behind research participation and product use to recognize how individuals are invariably influenced by household and community sociocultural circumstances and their influence on product acceptability and adherence.

Women reported experiences with ring use provided insight into how women understood the vaginal ring to work and how they chose to incorporate it into their lives. Despite its partial efficacy, women depended on the ring to protect them from HIV highlighting the need for healthcare providers to emphasize and ensure comprehension about the varying levels of product efficacy during delivery of different HIV prevention products in local communities – the ring being partially efficacious as compared to PrEP which has a high efficacy. There were some misunderstandings about how quickly or slowly protection was offered or maintained

when the ring was inserted or removed. Counselling and education around how the ring works to offer protection, its known efficacy and how it fits within a multi layered HIV prevention approach of different HIV prevention choices is important information that should be provided as the ring is rolled out in countries where it is approved for use (4, 5) in settings where the choice of oral and injectable PrEP may also be offered.

Women had the option to decline the ring during HOPE, however many chose to accept the ring and thereafter reported challenges with adherence suggesting that some women may have joined the OLE study for the benefits received through study participation vs. ring benefits.

Important motivators to ring use and challenges experienced were reported. The most common reasons for ring removal being menses, partner objection and perceived side effects and the main reasons reported for consistent ring adherence were support from others, confidence in the ring providing protection from HIV and the ring enhancing sexual experiences, all similar to previous findings among women who participated in ASPIRE (6, 7, 8, 9). Women's experience with ring use during ASPIRE and HOPE were similar regardless of the rings proven efficacy following ASPIRE and the difference in both study designs.

Women with low residual drug level results cited distrust of the testing method of the ring and questioned the accuracy of the results. Testing of returned rings provided an estimate of ring use and were not 100% precise possibly due to the variability of the tests in detecting small differences in the amount of drug remaining in the ring and the rate of release being affected by differences in absorption, the vaginal environment and behavioural factors such as removals and re-insertions (10). Residual drug level testing may not be feasible in program settings and has its limitations however researchers should look at which adherence strategies, such as real time adherence monitoring, adherence support programs and self-reported adherence, work to address adherence challenges (11).

Although the findings echoed other research findings about ring experiences (6, 7, 8, 9), some important differences were noted – motivations to join research did not necessarily translate to vaginal ring use, although it was only partially efficacious women still chose to use it for protection and even though women had a choice to decline the vaginal ring, they still opted to accept it but ultimately had challenges with use. This tells us that structural and social determinants still play a role in clinical research.

The key points from the narratives are indicative of an ecological model where both individual levels of influences and social environmental levels of influences impacted decisions and actions when it came to study participation and ring use. Individual levels are perceptions, beliefs, or attitudes, household levels are influences from partners, peers and family, organizational levels include influences from the work, economical and health structures, and the community level is about influences around community norms and beliefs as well as perceptions about HIV (12) (Figure 4). Figure 5 shows how their decisions and actions links with these levels of influences.

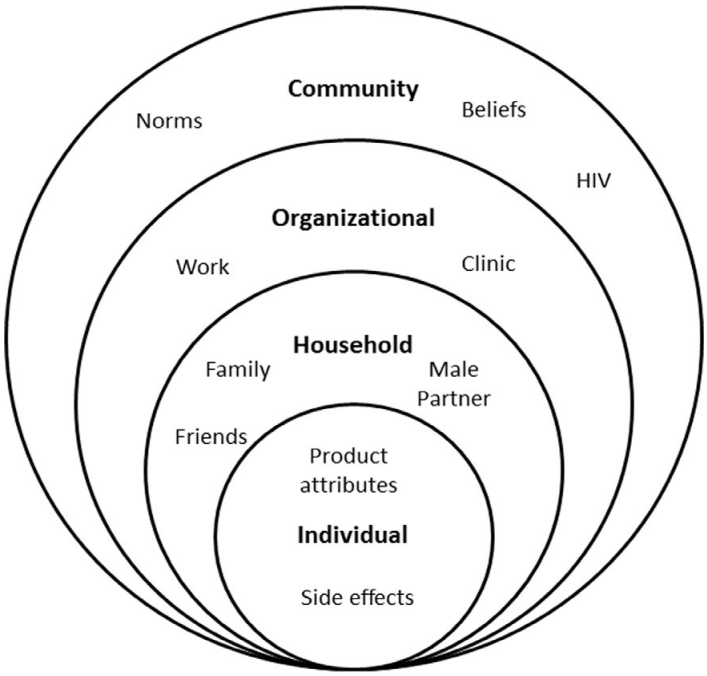

Figure 4: Socio-ecological model of factors affecting adherence in VOICE, and levels of influences

(Source: Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa by A. van der Straten, J. Stadler, E. Montgomery, et al. PloS one. 2014 Feb 21;9(2): e89118)

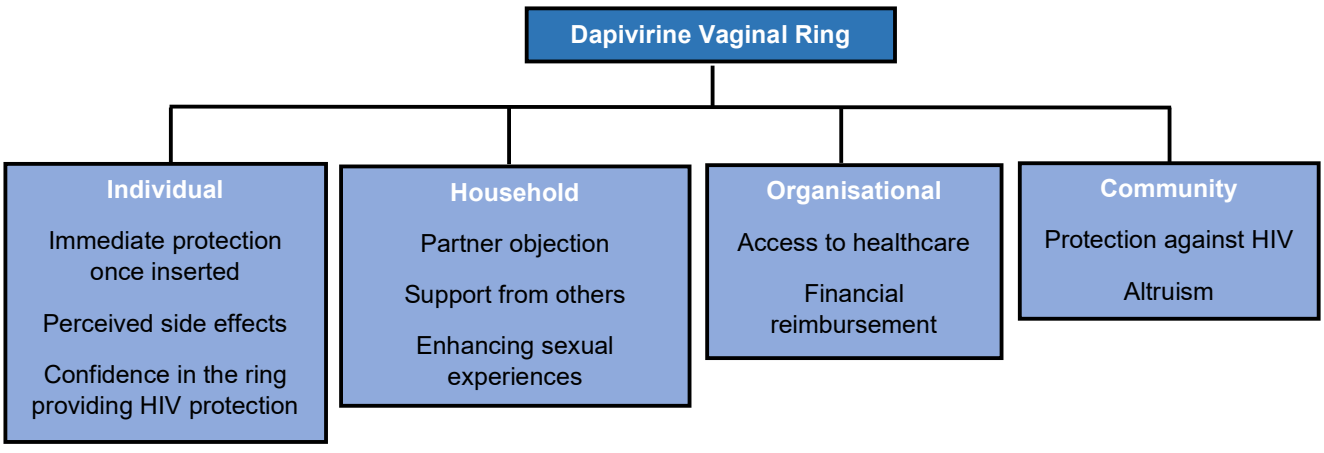

Figure 5: Relationship between women's narratives and the different levels of influences (individual and social environmental)

What we are seeing is related to Urie Bronfenbrenner's ecological systems model (13) where human beings and their interactions with their environments contributes to human development. The foundation of Bronfenbrenner's ecological model are levels of environmental influences that expands outward towards social systems of influence. These levels are divided into five systems – the first level of influence is the microsystem which includes interpersonal interactions among family, friends and peers, the second level of influence is the mesosystem which are the relationships between the different microsystems like the interaction between family and friends, the third level of influence is the exosystem which includes larger social structures such as communities and local governments, the fourth level is the macrosystems which consists of cultural characteristics, beliefs, social norms and socioeconomic factors (13, 14).

Health behaviour is complex with multiple factors and the narratives provided by women in the OLE study confirms this. Understanding the various social environmental factors, beliefs, perceptions and attitudes amongst women and how it affects one's health behaviour can provide a platform to inform public health agendas, help recognize the most significant factors for a particular person or population and enable program designers to focus on the most relevant issues (15). Implementing individual level behaviour change interventions may encourage people to take action to improve their health however, a multi-pronged holistic approach is needed to speak to the complexity of the levels of influences that exist beyond the "silo" of only the individual level (12, 16).

The urgent need to address these influences through concomitant interventions that speak to the multiple levels of influence will support an individual's use of and adherence to HIV prevention products. This could be in the form of provider training, community health fairs, male and community engagement activities, peer group support and motivational workshops.

These narratives provide valuable information that can be used in the future rollout of the vaginal ring and other HIV prevention products in Africa. It can also be used to inform implementation of future projects and delivery programs like the Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC) project (17). The Catalysing Access to New Prevention Products to Stop HIV (CATALYST) study under the MOSAIC project will be assessing the implementation of providing the choice of oral PrEP, PrEP ring, and injectable cabotegravir for PrEP among women at more “real world” public health clinics in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe (17).

AGYW remain a key population affected by HIV in sub-Saharan Africa (18, 19). Women need a variety of HIV prevention options, like contraception, that can be used with different partners at different periods of their lives (20). Although HIV prevention research amongst women has progressed substantially over the years, important biomedical, behavioural, and social science factors still play a role in the prevention of HIV infection among women globally (20). Addressing and understanding these factors together with the provision of current and future HIV prevention options to women will result in a global decline of HIV infections among women and progression towards the United Nations (UN) goal of ending the AIDS epidemic by 2030.

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APPENDIX I: MTN 032/AHA Study Part 2 Sample Informed Consent Form

MTN-032

Assessment of ASPIRE and HOPE Adherence

Version 2.0

PHASE 2 (HOPE) PARTICIPANTS

September 5, 2017

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Assessment of ASPIRE and HOPE Adherence

INFORMED CONSENT

You are being asked to take part in this phase of the research study because you are a woman who participated in the MTN-025 (HOPE) trial and received the dapivirine vaginal ring during your trial participation. Up to 156 women will participate in this second study phase at multiple HOPE 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 continue in this study, we want you to learn more about Phase 2 of the MTN-032 study. This consent form gives you information about Phase 2 of this study. Study staff will talk with you and answer any questions you may have. Once you read and understand Phase 2 and its requirements, you can decide if you want to take part in the second phase of this trial. If you do decide to continue in this study and take part in Phase 2, 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 Phase 2 of this study will then be assessed, and once confirmed, you will be considered enrolled in Phase 2 of the MTN-032 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 for more information).

WHAT IS THE PURPOSE OF THIS STUDY?
You are being asked today to take part in Phase 2 of MTN-032. The main goal of the second phase of this study is to better understand HOPE participants' use of study product (vaginal rings) while participating in both the ASPIRE and HOPE trials. Women who completed the HOPE trial may be eligible to participate in MTN-032 Phase 2.

Some Phase 2 participants will be asked to participate in an in-depth interview (IDI), and some will be asked to participate in a focus group discussion (FGD) with other participants. Participants will be asked questions individually or in a group setting. Study staff will tell you if you are going to take part in an IDI or FGD.

To obtain information about your participation in ASPIRE or HOPE, the MTN-032 study team will need to review your ASPIRE and/or HOPE research records. By signing this form, you are giving the MTN-032 study team permission to access your research records.

STUDY PRODUCTS
There are no study products (investigational drugs or other products) involved in this research study.

STUDY PROCEDURES
Phase 2 of the MTN-032 study consists of one study visit, including the Screening/Enrollment Visit which is taking place 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 questionnaires that will help researchers better understand your interview responses.
- You may be asked to have an in-depth interview (IDI):
    - You will have an IDI in the presence of one or two MTN-032 research staff members. The IDI will take approximately ***[SITE TO INSERT TIME]***. Clinic staff will make every effort to ensure your privacy and confidentiality.
    - During the IDI, the interviewer will talk with you about your HOPE adherence results.
        - Adherence refers to whether HOPE study participants used the dapivirine vaginal ring as instructed by trial staff.
        - In HOPE, a participant's adherence levels were measured by the amount of study drug (dapivirine) that remained in returned vaginal rings, and adherence was discussed during counseling and interview sessions.

- The interviewer will then ask more questions, and may take notes and will audio-record your conversation. Interviews will be audio-recorded to make sure we record your words exactly how you said them.
- You will be asked some general questions, such as your age, education, living situation, relationship status, and health.
- The interviewer will also ask you questions about:
  - Your experience with ring use and HOPE trial participation.
  - Your motivations for participating in HOPE.

- You may be asked to participate in a focus group discussion (FGD). If you're asked to join a FGD:
  - The FGD will take approximately ***[SITE TO INSERT TIME]***. Study interviewers/facilitators will lead the discussion, fully explain the process, and answer any questions you have.
  - Before the FGD begins, the interviewer will talk with you in private about your HOPE adherence results.
    - Adherence refers to whether HOPE participants correctly used the dapivirine vaginal ring as instructed by trial staff.
    - In HOPE, a participant's adherence levels were measured by the amount of study drug (dapivirine) that remained in returned vaginal rings, and adherence was discussed during counseling and interview sessions.
  - In a small group setting with other study participants, an interviewer will encourage discussion of various topics similar to those discussed during the IDIs. The interviewer will also encourage discussion about the results of the HOPE trial and about possible educational and marketing approaches to promote ring use.
  - Like the IDIs, FGDs will be audio-recorded and later transcribed.
  - A study staff member will take notes during the discussion as a backup to the audio-recording.
  - You will be asked to use fake names for yourself and anyone you talk about.
- Study staff will also:
  - Inform you about other services, if needed.
  - Schedule your next visit, if necessary.
  - Reimburse you for your visit(s).

RISKS AND/OR DISCOMFORTS

During the interview or focus group discussion, you may be asked some questions that cause you to feel embarrassed or uncomfortable. You may become embarrassed and/or worried when discussing sexual practices or your use of the vaginal rings. Trained study interviewers will help you deal with any feelings or questions you have. You can choose not to answer questions 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, IDIs 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-032 interview team will be able to link your responses to you personally. The 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-032 study team for the purposes of this research. Your voice recordings will also be kept in a secure location and only people involved with the study will have access to these recordings. Study leaders will make sure this happens.

If you participate in a focus group discussion, 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 at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private.

However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. 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. Information participants provide may help researchers improve counseling materials about product use and sexual behavior. Lastly, the information provided in this study may help health professionals develop ways to 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. The study staff may use your personal information to verify that you are not in any other research studies. This includes studies conducted by other researchers that study staff may know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:
- The Research Triangle Institute
- Site IRBs/ECs
- FHI 360
- Representatives of the US Federal Government, including the US OHRP, NIH and/or contractors of NIH, and other local and US 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: MTN 032/AHA Study Part 2 Female In-depth Interview Guide

MTN-032 Part 2

Female In-depth Interview (IDI) Topic Guide

INSTRUCTIONS for the Interviewer: How to use the IDI Guide

9. Section topics are in shaded in gray and **bolded**.
10. *Instructions/suggestions to interviewer are in italics and [brackets].*
11. Not ALL questions need to be asked. It is up to the interviewer's discretion if a question should be skipped if the participant has already provided a response to the question earlier in the interview. Please ensure that by the end of the interview, all the topics and key themes have been covered.
12. Purpose statements should be considered notes to the interviewer and are not meant to be read aloud. They explain the reason for asking that question or set of questions in order to provide more context to the interviewer who can then rephrase in her own words or clarify to the participant as necessary.
13. There are two levels of questions:
    a. Primary interview questions: appear in **bold** text. They address the topics that you as the interviewer should ask and discuss with participants. You are not required to read them verbatim, but they are written to ensure some consistency across IDIs.
    b. Probing topics are indicated with a bullet. If you find that the participant does not provide much information in response to the primary question, these probing topics may be used to encourage further discussion. Probes with the words "*KEY PROBE*" written before it are probes that are the most important to try to address. Depending on what has already been discussed, and the IDI context, you may or may not ask the rest of the probes.
14. Words found in (parentheses) are meant to provide wording options to interviewers to fit various situations. For example, they often provide a present or past tense verb.
15. The IDI guide is not meant to be used to take notes. Rather, you should use the separate notes form, where you will also insert your initials, the participant's PTID, as well as the date, start and end time of the interview.
16. **Special note about seroconverters:** It is important for study staff to review the participant's HIV status before conducting any study procedures. When asking questions to seroconverters, start off by emphasizing that confidentiality is maintained in the study and reassure the participant that her study information will not be shared with anyone outside the study. Then inform the participant that you are aware that she has seroconverted.

Before starting the IDI, ensure the participant has provided written informed consent.

[*Start Recorder and Read Introduction*]: **My name is _____. Thank you again for your willingness to be in this study. The main goal of this discussion is to better understand your experience participating in HOPE. I want to remind you that there are no right or wrong answers, and what we discuss here will be kept confidential; we will not share your personal information or responses with anyone outside of the study.**

If during our discussion, there are issues or concerns that you would like to talk about, feel free to bring them up; I will take note of them and answer them directly after the interview. If I cannot answer them, I can refer you to someone who may be able to help. Before we start, can you confirm for the recorder that you have already provided written informed consent to take part in this discussion? [*Wait for oral confirmation to begin*].

I. Motivation for joining HOPE

Purpose: To get details about all of the reasons why she joined HOPE and whether she was influenced more from the ring or the study benefits.

22. What are the reasons why you joined HOPE?

Possible probing topics:

- *KEY PROBE:* What were you hoping to gain from HOPE? Did you get what you came for? Please explain.
- *KEY PROBE*: Did you join HOPE more because of the ring or more because of the benefits you received from the study? Please explain.
- *KEY PROBE*: What concerns did you have about joining HOPE?

23. How important did you feel it was to discuss whether to join HOPE with someone else? Why?

Possible probing topics:

- *KEY PROBE*: With whom did you actually discuss? Why? How did they react?
- *KEY PROBE*: How did you get them to accept your decision to participate (if applicable)?
- *KEY PROBE*: How did their opinions influence your decision?
- Why did you not discuss with (others not mentioned above)?

24. How has being part of HOPE affected you emotionally or socially?

Possible probing topics:

- How has being in HOPE made you feel about yourself? (describe feeling and if positive or negative?) Why?
- Tell me about any positive or negative social experiences. (What happened, why, how did you feel? Etc.)

J. Ring Efficacy

Purpose: Find out her current understanding of how the ring works with different types of use and how that influenced her ring use.

25. I know you were told how to use the ring, but now I want to know in your own view how you THINK you need to use the ring to get your desired level of protection from HIV? *(e.g. only when going to have sex, throughout the full month, intermittently depending on whether you feel at risk, etc.)* **Please explain.**

Possible probing topics:

- *KEY PROBE*: How are these beliefs the same or different from how you actually used the ring in HOPE?
- *KEY PROBE***:** What are other ways of using the ring that you heard about?

26. Did you think you needed to be protected all the time in HOPE? Please explain.

Possible probing topics:

- *KEY PROBE:* How did this influence your use of the ring? (*i.e. did you keep it in all the time even if you didn't feel you needed protection? or did you remove at times when you didn't feel like you needed protection?)*
- *KEY PROBE:* If you took the ring out to have sex for a few hours, how protected would you feel? Please explain.
- *KEY PROBE:* If you took the ring out and didn't have sex during that time, how protected would you feel the next time you had sex? Please explain.
- *KEY PROBE:* If you removed the ring to clean it, how protected would you feel the next time you had sex? Please explain.

27. How do you think the ring works in your body?

Possible probing topics:

- How fast do you think the ring provides protection after insertion?
- How fast do you think your protection decreases after removing?
- When you think about the drug in your body, how does that make you feel?
- How well do you think the ring protects against HIV?
- Do some people need more or less drug to be protected?
- What do you think affects how much drug is in one person's body compared to another person?

K. Drug results; Adherence/non-adherence; Ring influence on sexual activity

Purpose: To explore her reaction and understanding of her drug results from HOPE and explore the factors that influenced the participants' adherence or non-adherence in HOPE.

We would like to look at all of your results throughout HOPE and discuss them with you. Here are your results… [*Present over-time tool*]

28. How do you feel about these results?

Possible probing topics:

- What do these results mean to you?
- Do these results match with how you remember using the ring throughout HOPE? Why or why not? [*record on PSF if matches/does not match*]
- Do you trust the method used to test the rings? Why or why not? [*record on PSF if trusts/does not trust*]

29. Tell me about your sex life while in HOPE.

Possible probing topics:

- How many sexual partners did you have while in HOPE? (Same or different as in ASPIRE?)
- What kind of partners were they (*i.e. primary, casual, client, etc*.)?
- What kind of sex did you have with each partner (vaginal, anal, oral)? How often?
- What kind of sex did you have during menses?

30. Women differ in whether they feel comfortable talking to their partners about the ring. What did your partner(s) know about the ring, if anything?

Possible probing topics:

- Did you tell your partner(s) or how did he find out?
    - How did you bring it up?
    - How did he react?
    - How did his reaction affect your use of the ring?
    - Did his feelings about the ring change over time? What caused the change?

31. How did the ring affect your sexual life, if at all?

Possible probing topics:

- *KEY PROBE*: How did the ring affect sexual pleasure? (for you and your partners)
- *KEY PROBE*: Did you or your partner ever feel the ring during sex? Please explain a situation when this happened.
- *KEY PROBE*: How did your partner influence your ability to use the ring?
    - Did you sometimes remove the ring for sex? If yes, why? If no, why not?
    - If removed for sex, where did you put it? When did you re-insert the ring?
    - Did you do anything to avoid feeling the ring during sex? [*Ask about sex positions or acts;* foreplay/finger]
- If there were changes in your sex life, do you think they were good or bad? Why so?

32. What were the barriers to using the ring consistently?

Possible probing topics:

- *KEY PROBE*: [*If applicable*] How did it make you feel when you had a "0", "1", or "2"?
- *KEY PROBE*: When was it the hardest to use the ring? Why? What did you do to overcome the barriers?
- *KEY PROBE*: What kept you participating in HOPE despite the barriers you experienced?
- *KEY PROBE*: What motivated you to use the ring despite the barriers you experienced?
- *KEY PROBE*: How at risk did you feel during these times (when not having a 3)? Why?
- How did receiving 3 rings affect your ability to use the ring? (e.g. easier or harder) Why?

[NOTE: If participant consistently had 2's and/or 3's, ask question 12, otherwise skip to Section D.]

33. What was motivating you to use the ring during this time? (e.g. desire to protect yourself from HIV, desire to help the community)

Possible probing topics:

- *KEY PROBE*: [*If had any 3's*] How did it make you feel when you had a "3"?
- *KEY PROBE*: [*If had any 2's*] How did it make you feel when you had a "2"? Why?
- *KEY PROBE*: When was it hard to sustain this level of protection? Why? What did you do to overcome the barriers?
- Did you ever remove the ring during this time, even though you achieved "2's" and "3's"?
- How important was it to you to see high protection levels? Why was it so important?

L. Participant Engagement Activities & Study Procedures

Purpose: To gain insight on usefulness of site engagement activities at improving adherence.

34. What clinic events did you participate in during HOPE? *(e.g. group adherence meetings, social events, waiting room discussions, etc.)*

Possible probing topics:

- How often did you attend the events? [Be specific about what the event was.]
- What did you hear or talk about during the events with other participants? Describe what came up.
- What was it like to interact with staff during these events?
- What was it like to interact with other participants?
- Did you discuss what occurred during the events with other participants or other friends/family/members of community?
- What other activities you would have liked to have been offered?
- What did you hear from staff or others about ring use at your clinic?

35. How did the clinic events influence your ring use and/or feelings about the ring?

Possible probing topics:

- How were the activities helpful or not helpful in addressing:
  - Yours or other participants' perceptions of ring?
  - Yours or other participants' worries (side effects, harm) about the ring?
  - Trust or mistrust of medical research or healthcare?

M. Ring acceptability

36. What is your current opinion of the dapivirine ring? [U*se opinion tool*]

Possible probing topics:

- All the things you disliked (and why)?
- All the things you liked (and why)?
- How did your attitudes about the ring change over time in HOPE?
- What would make you like it more?
- What is your primary partner's opinion of the ring?
- What were the attitudes of other participants while in HOPE? How did this affect your thoughts about the ring?
- What were the attitudes of other people you told about your ring? How did this affect your thoughts about the ring?

N. HIV Worries and HIV Protection

Purpose: To gather more in-depth information about her HIV risk perception and risk reduction strategies.

37. How worried were you about getting HIV while in HOPE?

Possible probing topics:

- KEY PROBE: What increased or decreased your worry in HOPE? (e.g. *multiple partners, ring use, condom use, seropositive partner, drug/alcohol use, receiving money/goods for sex, HIV testing, etc.*)?
- *KEY PROBE*: How do your worries about HIV compare to other worries in your life (*e.g. financial, work, partner relationship, family issues, etc.*)?
- *KEY PROBE*: How did your concern about HIV affect your ring use?

38. What are you doing to protect yourself from HIV now that HOPE has ended? (*e.g. condoms, HIV testing, PrEP, medical male circumcision, mutual monogamy, etc.*)

Possible probing topics:

- *[Skip for seroconverters]* Do you think you will get HIV? Why/why not?
- How motivated are you to stay HIV free?
- *KEY PROBE*: What do you think about waiting for the ring to be approved by your government before it is available to you?
- Are you more worried about getting HIV from your primary partner or from someone else? Please explain.

O. Ring uptake, marketing and product roll-out

39. We hope the ring will be widely available in the future. If it is, what would make you interested in using it? *[Skip for seroconverters]*

Possible probing topics:

- *KEY PROBE*: What percentage of protection/ efficacy would the ring need to provide in order for you to use it in the future?
- *KEY PROBE*: How would you prefer to use the ring (e.g. wear at certain times or all the time)?
- What support would you need to help you use it?
- Where would you want to get the ring?

40. What about others – if the ring is widely available, what do you think will be important to others to make them want to use it?

Possible probing topics:

- What would encourage their interest and make the ring appealing to them?
- Do you think it will be popular – with whom?
- What concerns would they most likely have?
- What advice would you give to overcome these concerns?

P. Wrap Up and Closing Remarks

41. We have talked about a lot of things today. Thank you for taking the time to talk to me and share your opinions. We truly appreciate your willingness to participate and discuss your experience with us. You've been with us for a long time now – so many years -- and we are grateful for your commitment to this research and to helping us move the ring forward in science. Before we end, I want to give you the chance to tell us anything else you think we should know about the ring – good things, bad things, challenges with using it – anything, that will help us better understand the truth about this ring.

42. Do you have any questions for me?

APPENDIX III: MTN 032/AHA Part 2 Codebook

Parent Code	Child Code	Definition
TRIALS		Anything about the ASPIRE or HOPE trials including her experience as a trial participant. Anything about the ASPIRE results or thoughts or feelings about HOPE ending, or differences between ASPIRE and HOPE. Include anything they reported that happened between ASPIRE and the start of HOPE. Use this code when comparing differences between ASPIRE and HOPE study design or procedures.
	JOIN/ REMAIN	Discussion around participants' motivation to join and remain in HOPE. Include any discussion about joining or remaining for the ring, incentives -- monetary or health -- or any other. Include discussions about joining with others and about why she continued to participant despite barriers to ring use or lack of support. Double code with BARRIERS, SUPPORT or appropriate PEOPLE code as needed.
	SOCIAL/ EMOTIONAL IMPACT	Anything about how being in HOPE made the participant feel internally (emotionally) about themselves or how it affected them socially, including feelings about receiving their drug feedback. Also include discussion about feelings of altruism for joining the study or being a participant in the study. Include positive or negative experiences or feelings.
	ACTIVITIES	Anything about HOPE-organized activities such as tea parties, workshops, outreach events, male partner activities, etc. designed to address participant adherence and retention. Include discussion about the events influencing ring use or feelings about the ring. Includes description of actual or desired community engagement and education activities.
	CLINIC/ VISIT	Anything to do with the ASPIRE/HOPE clinic environment in general. Include anything with attendance or lack of attendance of ASPIRE/HOPE visits, keeping/missing appointments, duration of visits. Include discussions of monthly or quarterly visits.
	SITE-LEVEL FEEDBACK	Use for discussions about the feedback sites gave participants about the overall site's adherence performance (not individual results) in ASPIRE or HOPE. Use for discussions about receiving interim HOPE results as well.
RING		Anything about the ring that is not previously covered under the child codes. If discussing how the ring changed sex life, double code with SEX. Include discussion around storing rings at home or issues storing rings at home.
	EFFICACY	Apply to discussions of product efficacy, either actual, perceived, or desired including when a participant talks about feeling protected from the ring. Should be used to capture discussions about how she thinks she needs to use the ring to get the protection she desires.
	MECHANISM OF ACTION	Apply to discussion about how participants think the ring works to prevent HIV, including how it works in her body or others' bodies. Use when participant talks about how quickly or slowly the ring provides protection before insertion and after removal.
	OPINION NOW	Anything about anyone's opinions (her or her partner or family/friends, etc.) about the ring NOW (at time of interview) including its characteristics, fear/ring worries about the ring, likes and dislikes.

Parent Code	Child Code	Definition
	OPINION PAST/ OVERTIME	Anything about anyone's opinions (her or her partner or family/friends, etc.) about the ring over-time (prior to time of interview) including its characteristics, fear/ring worries about the ring, likes and dislikes.
	SIDE EFFECTS/ PHYSICAL SAFETY	Apply to comments specifically about side effects and perceived side effects relating to the product from anyone who was exposed to the ring. Include discussion about physical safety of the ring including how the drug in her body makes her feel. If relates to feeling protected or being safe from HIV, code as EFFICACY.
	FUTURE	Code any discussion regarding willingness or plans to use (or not use) product in the future, in general not specific to any study. Include information about where they would want to get the ring in the future and how much they would be willing to pay and how often they would like to use the ring (all the time or intermittently). Include discussions about wanting to be (or suggestions on who should be) an advocate or champion for the ring. Include any recommendations or thoughts on who else would use or benefit from the ring if the ring became successful and what would make the ring appealing for others to use it as well as what concerns others may have about using the ring. Also include discussions about more general thoughts about the future post-trial.
ADHERENCE		Code anything not already under the child codes about adherence to the ring.
	INITIATION/FIRST USE	Anything about initiating ring use, either at the beginning of ASPIRE, HOPE, or after a period of dis-use. Include discussion about getting used to the ring, any issues, or lack of issues.
	USE	[About physically using/not using the ring]. Anything about using the ring or not using the ring. Include instances of removals (e.g. to clean or show others) or persistence with ring use and inserting/replacing the ring every month. Use this code for ring removals if the intention is to still use the ring (remove for less than a day). Use the DISCONTINUATION code if she talks about intentionally stopping ring use.
	BARRIERS	Apply when participant describes barriers she experienced during the HOPE trial to using the ring consistently. Include any difficulties with using the ring and how overcame these barriers. Double code with REMAIN or RISK as needed. For hypothetical barriers to using the ring in the future use FUTURE code.
	MOTIVATIONS/ SUPPORT	Apply when participants describe any motivations or reasons they are able to adhere to the ring or change her ring use (or things they think could have helped during HOPE trial), including any support she received from others, tools or reminders used to remember to change the ring, or a personal sense of altruism to use the ring for the benefit of other women/society. Double code with appropriate PEOPLE codes as needed. For hypothetical motivations or support for using the ring in the future use FUTURE code.
	DRUG FEEDBACK	Apply to discussion around her individual drug level results. Include what her results were and what they mean to her (how she understands them) as well as how important it was to her to receive a certain level (0-3).

Parent Code	Child Code	Definition
	(DIS)AGREEMENT	Use for whether the participant agrees or disagrees with the results (i.e. whether they match how she remembers using the ring or not). (Child code of DRUG FEEDBACK)
	DRUG TESTING	Use for whether she trusts the method of testing the ring or not and any complaints about the timing of getting the results back. (Child code of DRUG FEEDBACK)
	DISCONTINUATION	Code any discussion of discontinuing ring use, due to voluntary or clinical reasons for shorter or long periods, with the intention of stopping ring use (even if she later changes her mind), for a minimum of a day. May include pregnancy, HIV sero-conversion, etc. If discussing thoughts about the study ending, use the TRIAL code. Use the USE code instead for instances of removal where she still intends to use the ring.
HIV		Anything about HIV or AIDS. Includes HIV testing outside of the trial setting. Use TRIALS if talking about HIV testing in ASPIRE/HOPE.
	RISK	Any discussion of perceived vulnerability of HIV and risk behavior or situations, including sexual risk, multiple partners, partner has other partners, other risk behavior (drugs/alcohol, pregnancy risk), unknow HIV status of partner or risk in general (i.e. having a reckless behavior, or being in a risky situation). Includes perceived lack of risk. Also includes discussion about HIV worries, including what influenced worry and timeline or changes in level of worry (before HOPE, after, etc.). If talking about feeling protected from the ring, use EFFICACY. The risk does not have to be blatantly identified by the participant, can be interpretative by coder. Double code with appropriate PEOPLE codes as necessary.
	PREVENTION METHODS	Anything about methods she is using, has used or plans to use to prevent HIV besides the ring or in combination with the ring. Could be male or female condom, or other methods i.e. oral PrEP, monogamy, regular testing, etc. Also includes all practical aspects of condom use (i.e., use/non-use, storage, transport, etc.), preference for ring and/or other products.
HEALTH		Anything about health not related directly to the ring (if ring related use SIDE EFFECTS/ PHYISCAL SAFETY). Includes anything about sexual and reproductive health, menses, and fertility.
CONTEXTUAL / STRUCTURAL		Include discussion of the social, cultural or structural context in which the participant is living. May include local practices, urban/rural location, HIV prevalence, sociocultural norms, religion, local beliefs, traditional medicine, interaction with local clinics or non-study healthcare (including healthcare staff), or other discussions of the community. Include anything about employment (including sex work), work, school, studies, domestic work, etc. Use also for anything in place before the trials began (e.g. cultural aversions to trials overall).

Parent Code	Child Code	Definition
STIGMA/ MISCONCEPTIONS		Anything about any kind of rumors, gossip, stories (positive or negative), or stigma about research in general, ARVs, condoms, HIV prevention, HIV transmission, the HOPE study in particular (e.g. associated with Satanism or Witchcraft) or the ring or its formulation (e.g. it causes cancer). Include discussion about foreign researchers or white researchers as it applies to HOPE. Applies to external and internalized stigma/misconceptions.
SEX		Anything about her sex life, sexuality, sex practices (oral, vaginal or anal) or behaviors, including how the ring affected the sexual experience. Include comments about experience of discomfort or pain during sex and any mention of participant or partner either feeling or not feeling the ring during sex. Any comments about experience of pleasure during sex, either positive or negative. Any change in sexual practices as a result of ring use (different position, avoiding oral or digital sex, etc.). Applies to either her or her partner's experience.
DISCLOSURE		Anything about disclosing trial participation, product use/non-use, drug feedback results, or HIV status to anyone. Also includes disclosing information about relationships and sex partners. Include discussions of honesty, dishonesty, lying, secrecy, or hiding something. Double code with appropriate PEOPLE codes as necessary.
PEOPLE		Anything about groups of people who DO NOT fall into the child code categories (e.g. boss, coworkers, etc.). Include community groups that one may be a member of. If coworkers or boss, double code with CONTEXTUAL/STRUCTURAL.
	COMMUNITY / NEIGHBORS	Anything about neighbors or members of the community
	FAMILY	Anything about immediate or extended family members. Double code with PEERS if their family member is also a participant.
	MALE PARTNERS	Anything about male partners – husbands, boyfriends, casual partners. Include number, type, communication, and decision-making power, relationship dynamics, trust, etc. Double code with MOTIVATION/SUPPORT if partner helped her adhere to ring.
	PEERS	Include fellow participants and other friends not in the study, including housemates who are not family members. Anything about other women in the ASPIRE or HOPE trials. Include discussion/conversations with other participants before/during/after trial, in the waiting room, etc. Should be applied to specific discussions of other participant actions, conversations, etc., not to the general 'we'. Double code with FAMILY if their family member is also a participant.
	STAFF	Anything about HOPE and/or ASPIRE staff.
OPINION TOOL		Use for any discussion during the opinion tool (emoji stickers) activity.
VULVA/PENIS MODELS		Use for any discussion when the vulva puppets or penis models are used or discussed.

Parent Code	Child Code	Definition
SEROCONVERSION		Anything about the participant's personal experience sero-converting, including how one sero-converted, timing, and reaction.
PARKING LOT		Anything that does not fit into the above codes but we think may be a salient theme. To be discussed during coding calls regularly.
STAR		Star quote or star examples.

APPENDIX IV: Co-Authored Publications Relevant to the MTN 032/AHA Study

Montgomery ET, Katz AWK, Duby Z, Mansoor LE, Morar NS, **Naidoo K**, Tsidya M, Chitukuta M, Guma V, Tenza S, Leslie J, Garcia M, Naidoo S. Men's Sexual Experiences with the Dapivirine Vaginal Ring in Malawi, South Africa, Uganda and Zimbabwe**.** AIDS Behav 2021 Jun;25(6):1890-1900. PMCID: PMC8516082

Katz AWK, **Naidoo K,** Reddy K, Chitukuta M, Nabukeera J, Siva S, Zimba C, Montgomery ET. The Power of the Shared Experience: MTN-020/ASPIRE Trial Participants' Descriptions of Peer Influence on Acceptability of and Adherence to the Dapivirine Vaginal Ring for HIV Prevention. AIDS Behav 2020 Aug;24(8):2387-2399.PMCID: PMC8631948