



History of Rectal Product Use and Country of Residence Influence Preference for Rectal Microbicide Dosage Forms Among Young Sexual and Gender Minorities: A Multi-country Trial Comparing Placebo Douche, Suppository, and Insert Products

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Abstract

The DESIRE Study (MTN-035) explored product preference among three placebo rectal microbicide (RM) formulations, a rectal douche (RD), a suppository, and an insert, among 210 sexually active transgender people and men who have sex with men in five countries: the United States, Peru, Thailand, South Africa, and Malawi. Participants used each product prior to receptive anal sex (RAS) for 1 month, following a randomly assigned sequence, then selected their preferred product via computer assisted self-interview. In-depth interviews examined reasons for preference. We compared product preference and prior product use by country to explore whether geographic location and experience with the similar products impacted preference. A majority in the United States (56%) and Peru (58%) and nearly half in South Africa (48%) preferred the douche. Most in Malawi (59%) preferred the suppository, while half in Thailand (50%) and nearly half in South Africa (47%) preferred the insert. Participants who preferred the douche described it as quick and easy, already routinized, and serving a dual purpose of cleansing and protecting. Those who preferred the insert found it small, portable, discreet, with quick dissolution. Those who preferred the suppository found the size and shape acceptable and liked the added lubrication it provided. Experience with product use varied by country. Participants with RD experience were significantly more likely to prefer the douche ($p=0.03$). Diversifying availability of multiple RM dosage forms can increase uptake and improve HIV prevention efforts globally.

Keywords HIV prevention · Transgender · Sexual minority men · Acceptability · Microbicide

Resumen

El estudio DESIRE (MTN-035) exploró la preferencia de producto entre tres formulaciones de microbicida rectal (MR) de placebo, una ducha rectal, un supositorio y un inserto, entre 210 personas transgénero y hombres que tienen sexo con hombres en cinco países: los Estados Unidos, Perú, Tailandia, Sudáfrica y Malawi. Los participantes utilizaron cada producto antes del sexo anal receptivo (SAR) durante un mes, siguiendo una secuencia asignada al azar, luego seleccionaron su producto preferido mediante una autoentrevista asistida por computadora. Las entrevistas en profundidad examinaron los motivos de preferencia. Comparamos la preferencia de producto y el uso previo del producto por país para explorar si la ubicación geográfica y la experiencia con la forma farmacéutica impactaron la preferencia. Una mayoría en los Estados Unidos (56%) y Perú (58%) y casi la mitad en Sudáfrica (48%) prefirieron la ducha rectal. La mayoría en Malawi (59%) prefirió el supositorio, mientras que la mitad en Tailandia (50%) y casi la mitad en Sudáfrica (47%) prefirió el inserto. Los participantes que prefirieron la ducha rectal la describieron como rápida y fácil, ya parte de su rutina y que tenía el doble propósito de limpiar y proteger. Los que prefirieron el inserto lo consideraron pequeño, portátil, discreto y de rápida disolución. Los que prefirieron el supositorio encontraron que tenía un tamaño y forma aceptables y proveía lubricación adicional. La experiencia con

el uso del producto varió según el país. Los participantes con experiencia con duchas rectales tenían significativamente más probabilidades de preferir la ducha rectal ($p=0,03$). Diversificar la disponibilidad de múltiples formas farmacéuticas de

MR puede aumentar la aceptación y mejorar los esfuerzos de prevención del VIH a nivel mundial.

Introduction

Rectal microbicides, or topical products that are applied to the rectum to prevent HIV during receptive anal sex (RAS), have great potential as an HIV prevention method. Early studies have demonstrated that they can deliver high concentrations of HIV prevention medications at the site of HIV entry [1] and that they may be acceptable to individuals at high risk of acquisition who eschew systemic PrEP due to concerns about side effects and long term effects [2]. Understanding user preferences concerning vehicles and dosage forms for delivering a rectal microbicide (RM) is key to its adoption. While there is a burgeoning literature on acceptability of rectal douches for HIV prevention, little is known about other potential delivery forms such as suppositories or inserts. Nevertheless, experience using rectal products may be a proxy for acceptability.

Rectal product use, including rectal douching (RD), varies based on country. RD is common among men who have sex with men (MSM) who have RAS [3]. In a survey of over 3000 MSM in the US who engaged in recent RAS, 80% reported douching beforehand [4]. Prevalence of douching prior to RAS by MSM varies by region. In an international survey with 1339 participants (88% MSM) who engaged in RAS, 66% reported douching prior to RAS, with use highest in Europe (72%) and North America (71%), then in Africa (62%), and lowest in Asia (57%) and Latin America/Caribbean (40%) [5]. Other recent research found that douche use before RAS ranges from 80% in the United States (US) to 73% in Africa and 63% in Latin America [6].

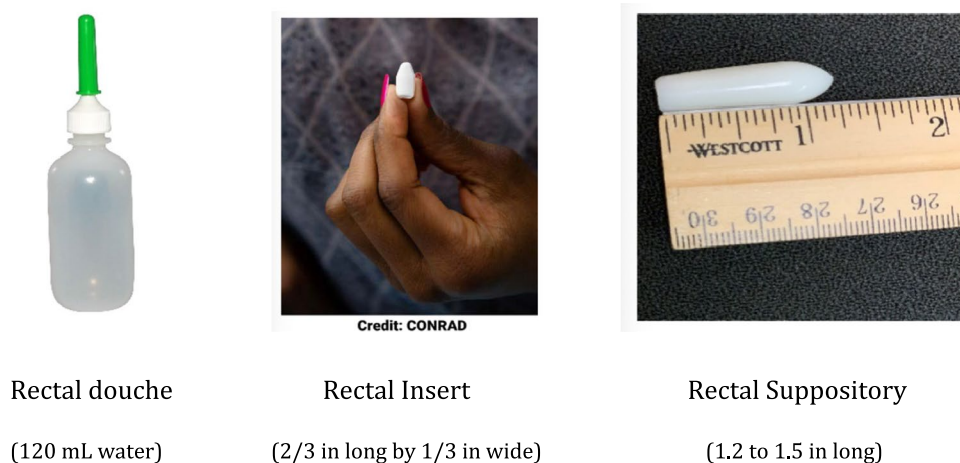
Devices used for RD also vary by country or region. Studies have found differing frequencies of use for enema bottles (50–77%), rubber bulbs (9–77%), attachable hoses (32–85%), commercial douche kits (6–31%), and plastic bottles (5–53%) [4, 5, 7–10]. In the US, enema bottles and rubber bulbs are more frequently used than attachable hoses, which are the most frequently used device for RD among participants in international studies [5, 9, 10]. Liquid used for RD also varies. The great majority of RD users use plain water for douching (59–89%), while others use water with soap (10–27%), water with salt (5–9%), or commercial preparations (6–30%) [4, 5, 7–11]. In one international study representing 112 countries [5], participants reported using saline-based products (56%), mineral oil/glycerin-based

products (22%), and laxative-based products (19%), while among MSM RD users in Kenya, 31% reported inserting a moist cloth into the rectum [12].

In addition, reasons for douching in the context of RAS vary by region. In a study comparing participants in the US, Latin America, and Africa, a majority of participants in all regions reported douching to be clean, but a greater proportion of participants in Latin America and Africa douched believing it might prevent infections [6]. Some cross-sectional studies have found an association between RD and an increased risk of HIV and STI's [13, 14], so prevention in the context of douching is critical.

Given that RD is a common behavior prior to RAS for MSM, researchers have investigated the acceptability of a douche as a potential mode of delivering rectal HIV pre-exposure prophylaxis (PrEP) among MSM. Studies have shown the idea to be highly acceptable, ranging from 63 to 98% [4, 15, 16]. Carballo-Dieguez et al. found that among current douche users, 98% reported high likelihood of using an HIV prevention douche, while 95% of MSM who were not douche users reported they would likely use a douche that would protect against HIV. Even among participants who only engaged in insertive anal intercourse, 95% expressed support for a partner to use rectal douches to prevent HIV (and 63% reported having previously requested that a partner use a douche prior to RAS) [4]. In addition, Tingler et al. found that study participants who had a history of RD use were more likely to find a RM douche acceptable [17].

While the literature demonstrates that RD is popular but varies by region, less is known about the acceptability of other potential modes of delivering PrEP rectally, such as rectal suppositories or inserts. Rectal suppositories are commonly used to deliver medications for relief of pain or itching in the rectum, and are approximately 1–1.5 inches long, made up a fat-based, fast release material (See Fig. 1). Limited research on the acceptability of the rectal suppository indicates that, among women and men at risk for HIV who have RAS in the US, the rectal suppository is acceptable for HIV prevention and was found to be easy to use [18]. Rectal inserts are solid tablets, approximately 2/3 of an inch long, and are fast dissolving (See Fig. 1). Even less research exists on acceptability of a fast-dissolving rectal insert as a microbicide, although several inserts are under development [19] and some have shown high efficacy in preclinical and clinical ex vivo models [20, 21]. Most recently, the MTN-035 DESIRE study found that, overall, a majority of participants in a multi-country study found rectal inserts (72%),

Fig. 1 Study products

suppositories (66%), and enemas (73%) highly acceptable as RM formulations [22].

Given the variability in RD by region, including devices, liquids and reasons used, rectal pre-exposure prophylaxis (PrEP) products that appeal to people in one region may not appeal to those in another, whether due to cultural factors (e.g., stigma surrounding same sex behavior and need for privacy), geographic factors (e.g., extreme heat), or prior use of similar rectal products. To ensure sufficient global uptake of rectal microbicide products, an understanding of how and why product preferences vary by country is useful for both product development and marketing. Therefore, we conducted a secondary analysis of computer assisted self-interview (CASI) and in-depth interview (IDI) data from the MTN-035 DESIRE study, a multi-country RM trial comparing the acceptability of a rectal douche, suppository and insert as delivery agents for rectal PrEP products. We aimed to compare product preference by country and to examine the reasons for these preferences, including whether prior experience with similar rectal products impacted them. Our findings can guide customization of

product development and culturally appropriate messaging internationally.

Methods

Sample

HIV-uninfected cisgender men and transgender people who have sex with men between the ages of 18 and 35 were recruited by local study sites from a variety of sources, including outpatient clinics, universities, community-based locations, online websites, and social networking applications. In addition, participants were referred to the study from other local research projects, research registries and other health and social service providers. Each study site selected the most appropriate recruitment strategies based on local contexts. Two-hundred and ten participants were randomized into six, three-period placebo product use sequences with varying product use order [22]. Product delivery systems included a rectal douche, suppository, and insert (see Table 1).

Table 1 Study product regimen sequence

Sequence	N	Period 1 (4 weeks)	Washout period (~ 1 week)	Period 2 (4 weeks)	Washout period (~ 1 week)	Period 3 (4 weeks)
A	35	Rectal insert	–	Rectal douche	–	Rectal suppository
B	35	Rectal douche	–	Rectal suppository	–	Rectal insert
C	35	Rectal suppository	–	Rectal insert	–	Rectal douche
D	35	Rectal insert	–	Rectal suppository	–	Rectal douche
E	35	Rectal douche	–	Rectal insert	–	Rectal suppository
F	35	Rectal suppository	–	Rectal douche	–	Rectal insert

Data collection took place between April 2019 and July 2020 in the US (Pittsburgh, PA; Birmingham, AL; and San Francisco, CA); Thailand (Chiang Mai); Peru (Lima), Malawi (Blantyre); and South Africa (Johannesburg). Participants were recruited through clinic registries, community outreach events, social networking sites and word of mouth/referrals.

Inclusion criteria included men (cis or transgender) and transgender women between 18 and 35 years old (inclusive) at screening who were HIV-1/2 uninfected with a reported history of consensual RAS at least three times in the past 3 months and the expectation to maintain at least this frequency during study participation. The study was reviewed and approved by the Institutional Review Boards (IRBs)/Ethics Committees (ECs) at all participating institutions. This study was submitted to clinicaltrials.gov on September 14, 2018 and assigned number NCT03671239.

Study Procedures

Participants were screened for eligibility prior to enrolling in the study. All enrolled participants provided written informed consent and completed administrative, behavioral, clinical, and laboratory procedures. At all clinic visits, participants were also offered condoms and lubricant. Participants were provided with their first rectal product for period 1, based on assigned sequence, and asked to administer the product in clinic, under supervision of study staff to ensure proper use as instructed. Participant reimbursement was based on local guidelines and approved by the local Institutional Review Boards and Ethics Committees prior to study implementation.

Product Use Instructions

Participants were asked to use their assigned product between 30 min and 3 h prior to RAS during the 4-week period, or at minimum once per week in the event of no sex (See Fig. 1). They were provided with a douche bottle and multiple tips, a bottle of inserts, and a strip of single wrapped suppositories, for respective product use periods.

They were instructed to insert the douche tip approximately $\frac{3}{4}$ inch into the rectum and to slowly squeeze the bottle to allow the water to flow into the rectum. Then, they should remove the tip and stay in position until feeling the need for a bowel movement to release the liquid. The instructions for the insert and for the suppository specified that the products should be inserted, rounded end first, about 1 inch into the rectum, past the sphincter. Participants were instructed to then hold or clench their buttocks for a few seconds and, if possible, to remain lying down or seated for about 30 min to wait for it to

dissolve. While douches and inserts were to be kept at room temperature, suppositories needed to be stored in a cool, dry place.

Quantitative Data Collection Procedures

At the end of each 4-week period, participants returned to the clinic for the product use end visits (PUEVs), in which they completed brief acceptability and adherence questionnaires via CASI about the product they had most recently used. Questionnaires were programmed in all study languages, following translation and back-translation. After completing three product sequences, participants completed a termination visit which included a CASI survey and obtaining clinical results or treatment for urinary tract, reproductive tract or sexually transmitted infections, as needed.

Qualitative Data Collection Procedures

A subset of participants ($n = 70$; 10 per site) were invited to complete a video IDI using a password secure platform with trained qualitative interviewers located at a partner research institution. Only the audio portion of the IDIs was recorded. These final interviews followed a semi-structured interview guide informed by the RM product acceptability conceptual model proposed by Mensch et al. [23], which examines factors such as social, structural and partner context that influence product acceptability, product preference, and product adherence. The interviews lasted on average 60 min.

Interviewers included the first and fifth authors (RG and RT), as well as a team of New York-based researchers who were hired for the study due to being culturally and linguistically matched with participants. Interviews were conducted in each participant's native language. Interviewers were thoroughly trained on qualitative interviewing techniques such as use of open-ended questions, pauses and probing, and practiced extensively with the interview guide before working with participants. In addition, the team of female interviewers from international backgrounds participated in a training focused on sexual and gender minority sensitivity, including an orientation to anal sex and pleasure, as well as the legal and social contexts surrounding homosexuality in study site countries.

Quantitative Measures

Sociodemographic characteristics At baseline, we collected sociodemographic characteristics, including age, sex assigned at birth and current gender, race/ethnicity, sexual identity, relationship status, employment and educational attainment.

Prior use of rectal products At baseline, participants answered a series of questions that asked about their history

of rectal product use, including use of rectal douches/enemas, suppositories, and inserts. Products were described in the questionnaire as follows:

“A *rectal douche*, or enema, refers to water or a prepared liquid or substance that is inserted in your rectum or “butt” to clean it.”

“A *rectal suppository* refers to a solid medical preparation in a roughly conical or cylindrical shape, designed to be inserted into the rectum to dissolve.”

“A *rectal insert* is any object other than a suppository (e.g., soap) that you may have inserted in your rectum or “butt” to clean it.”

Ranking of product preferences Upon completing use of all three study products, participants were asked to rank the products in order of preference based on which would best fit with their lifestyle for HIV prevention.

Qualitative Measures

In-depth interviews The interview explored, among other topics, participants’ history of use of rectal products prior to their trial participation (“Prior to this study, had you ever used a suppository, enema or insert?”), experiences with the three study products throughout the trial including reason for product preference (“Which product did you like best, and why?”, “Which product did you like least, and why?”).

Quantitative Data Analysis

The sample was characterized using descriptive statistics such as means, standard deviations, and proportions. Fisher’s exact tests were performed to determine any differences in individual product preference, such as douche, suppository, and inserts, based on product use history and country. Statistical significance was set as a P-value less than 0.05. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Qualitative Data Analysis

Qualitative data collected via the IDIs were transcribed, cleaned to ensure accuracy of transcription, and translated to English by the interviewers who were all bilingual. Transcripts were loaded into Dedoose (V7), an online web application for qualitative data analysis within a team of three coders. Data on product preferences and prior rectal product use were coded and discussed for convergence. Discrepancies between coders were resolved with input from a third coder to reach consensus. The goal of the qualitative analysis was to provide greater context and understanding of the preferences identified in the quantitative data. The data were analyzed using content analysis, which enabled us to understand the context for product ratings based on country and

history of product use. Finally, the coding reports for product preferences and prior rectal product use were stratified by country and analyzed for country-specific themes using content analysis [24], and quotes were selected to illuminate the quantitative findings. We present the qualitative findings to provide context, noting that no inferences can be drawn about the prevalence of qualitative acceptability findings beyond this sample.

Results

Sociodemographic Characteristics

Participants were on average 25 years old, and a majority (99%) were assigned male sex at birth. At the time of the study, 80% identified as male, while 10% identified as transgender and another 10% identified as gender non-conforming or multiple genders. Among 96 participants at the US sites, the sample was racially and ethnically diverse with 13 (14%) identified as Latinx ethnicity, 16 (17%) as African-American, and 8 (8%) as Asian. Close to half of the South African participants (47%) identified as Zulu (See Table 2).

Based on our analysis, we present below the findings for each study product, including variations by country regarding product preferences and prior product use. We include quotes to illuminate the reasons for high and low levels of product preference by country.

Rectal Douche

Preference for Douche by Country

Based on the CASI questionnaire completed by all participants at the Final Visit, the rectal douche was the most preferred product in the United States (preferred by 55.6% of respondents), Peru (57.9%) and South Africa (48.3%) (See Table 3). A total of 70 participants completed the interview at the end of the study in which they were asked which product they liked best and why. We analyzed the qualitative findings by country and found some variations in reasons for product preferences.

Participants in the United States most frequently described the advantages of the douche as familiar and easy and they liked that it was a product that could help them be clean and protected all in one:

I could in theory, just replace the douche with the douche I was already using, so it wouldn’t necessarily like impact anything in, in terms of my preparation and my like sexual practices in general. (Transgender woman, 26 yo, San Francisco)

Table 2 Participants' sociodemographic characteristics, overall and by site

	All sites (N = 217)	Birmingham, USA (N = 33)	Pittsburgh, USA (N = 33)	San Francisco, USA (N = 30)	Blantyre, Malawi (N = 31)	Chiang Mai, Thailand (N = 30)	Johannesburg, South Africa (N = 30)	Lima, Peru (N = 30)
Age (years), M (SD)	24.9 (4.7)	25.7 (5.1)	25.5 (4.8)	28.6 (3.9)	24.6 (4.6)	23.3 (3.3)	21.9 (3.0)	24.7 (4.7)
Sex assigned at birth, N (%)								
Male	214 (99%)	31 (94%)	32 (97%)	30 (100%)	31 (100%)	30 (100%)	30 (100%)	30 (100%)
Female	3 (1%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gender								
Male	173 (80%)	28 (85%)	28 (85%)	27 (90%)	19 (61%)	22 (73%)	28 (93%)	21 (70%)
Female	2 (1%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Transgender male	2 (1%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Transgender female	19 (9%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	8 (27%)	2 (7%)	7 (23%)
Gender non- conforming/ variant	5 (2%)	0 (0%)	3 (9%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Other gender	10 (5%)	0 (0%)	0 (0%)	1 (3%)	9 (29%)	0 (0%)	0 (0%)	0 (0%)
Multiple genders	6 (3%)	2 (6%)	1 (3%)	0 (0%)	3 (10%)	0 (0%)	0 (0%)	0 (0%)
Latinx ethnic- ity (U.S. sites)	13 (6%)	2 (6%)	3 (9%)	8 (27%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Race (U.S. sites) or ethnic group (non-U.S. sites)								
Asian	8 (4%)	0 (0%)	2 (6%)	6 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black or African American	16 (7%)	13 (39%)	1 (3%)	2 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian or other Pacific Islander	1 (1%)	1 (3%)	0 (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White	66 (30%)	19 (58%)	28 (85%)	19 (63%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiple races	33 (15%)	0 (0%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	30 (100%)
Thai	30 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	30 (100%)	0 (0%)	0 (0%)
Xhosa	5 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (17%)	0 (0%)
Zulu	14 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14 (47%)	0 (0%)
Other African ethnic group	38 (18%)	0 (0%)	0 (0%)	0 (0%)	31 (100%)	0 (0%)	7 (23%)	0 (0%)
Other	6 (3%)	0 (0%)	0 (0%)	2 (7%)	0 (0%)	0 (0%)	4 (13%)	0 (0%)

It combined the medication and cleaning in one, so it was easy to do both. (Cisgender man, 26 yo, San Francisco)

Participants in Peru described preferring the douche because it helped them to feel clean, it was the best to use in conjunction with sex, and they found it easy to use:

I liked the douche more because of the cleanliness. It's much deeper, I feel lighter for when I have dates, if I have sex...I felt a little more pleasure, I had more libido. (Transgender woman, 27 yo, Peru)

In South Africa, participants found the douche easy, familiar, and they liked that they felt no side effects:

Table 3 Product preference by country

	Preferred product: douche (conjoint analysis, selection of preferred study product, BEST)			Preferred product: suppository (conjoint analysis, selection of preferred study product, BEST)			Preferred product: insert (conjoint analysis, selection of preferred study product, BEST)		
	No (n = 98)	Yes (n = 93)	P value	No (n = 149)	Yes (n = 41)	P value	No (n = 134)	Yes (n = 58)	P value
Country									
United States (n = 90)	40 (44.4%)	50 (55.6%)	0.14	73 (81.1%)	17 (18.9%)	0.0004	67 (74.4%)	23 (25.6%)	0.0027
Peru (n = 19)	8 (42.1%)	11 (57.9%)		15 (79.0%)	4 (21.1%)		15 (79.0%)	4 (21.1%)	
Thailand (n = 30)	20 (66.7%)	10 (33.3%)		25 (83.3%)	5 (16.7%)		15 (50.0%)	15 (50.0%)	
Malawi (n = 23)	15 (65.2%)	8 (34.8%)		9 (40.9%)	13 (59.1%)		21 (91.3%)	2 (8.7%)	
South Africa (n = 29)	15 (51.7%)	14 (48.3%)		27 (93.1%)	2 (6.9%)		16 (53.3%)	14 (46.7%)	

Bold values indicate statistically significant

I like the douche the best because it has been in my life ever since I was a baby (laughs)... Even after you are finished there are no after effects. I have mastered how not to have after effects after using it and with the other two products I had after effects. (Gender non-conforming, 22 yo, South Africa)

In contrast, some participants in Malawi reported finding the douche difficult to use, and they did not like that it was neither portable nor discreet:

You can't carry the douche around or put it in your pocket when going to the club or a tavern. Also, if it is discovered by someone in case I forget it somewhere, they would ask a lot of questions about it. (Cisgender man, 31 yo, Malawi)

In Thailand, participants who rated the douche as their least preferred product reported that, in addition to being less portable, they had problems with the applicator tip, described as “sharp and painful” and with squeezing all the water out of the bottle.

Prior Douche Use by Country

We hypothesized that familiarity with the product might influence preferences, so we also examined prior product use by country and the impact of prior product use on preference.

Via the baseline CASI, participants reported on experience using a rectal douche before RAS. Most participants in Malawi (69%) and half of those in South Africa had

Table 4 History of rectal product use by country

Baseline product use	United States (702, 764, 768) (n = 96) N (%)	Peru (715) (n = 32) N (%)	Thailand (791) (n = 32) N (%)	Malawi (760) (n = 29) N (%)	South Africa (805) (n = 30) N (%)
Rectal douche use before RAS					
Never used	25 (26%)	11 (34.4%)	3 (9.4%)	20 (69.0%)	15 (50.0%)
Infrequently	12 (12.5%)	3 (9.4%)	3 (9.4%)	2 (6.9%)	4 (13.3%)
Frequently	37 (38.5%)	8 (25.0%)	6 (18.8%)	1 (3.5%)	4 (13.3%)
Always	22 (22.9%)	10 (31.3%)	20 (62.5%)	6 (31.0%)	7 (23.3%)
Suppository use before RAS					
Never used	94 (97.9%)	29 (90.6%)	32 (100%)	28 (96.6%)	28 (93.3%)
Infrequently	2 (2.1%)	2 (6.3%)	0 (0%)	0 (0%)	0 (0%)
Frequently	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	1 (3.3%)
Always	0 (0%)	0 (0%)	0 (0%)	1 (3.5%)	1 (3.3%)
Insert use before RAS					
Never used	95 (99.0%)	31 (96.9%)	32 (100%)	25 (86.2%)	25 (83.3%)
Infrequently	0 (0%)	1 (3.1%)	0 (0%)	1 (3.5%)	2 (6.7%)
Frequently	1 (1%)	0 (0%)	0 (0%)	2 (6.9%)	1 (3.3%)
Always	0 (0%)	0 (0%)	0 (0%)	1 (3.5%)	2 (6.7%)

never used a rectal douche before RAS. Most common reasons given for not douching before RAS in Malawi included not having access (75% of those who had not douched) or not being sure how to douche (15%). In South Africa, not having access (60%) and having unplanned sex (40%) were primary reasons. Of note, several participants in South Africa made reference to having used an enema as a child, so they were not completely unfamiliar with the process, even if it was not a habitual activity before sex for some:

As a child I think I was nine or ten or even younger – traditionally when a kid is about to go back to school or about to go on holiday, you use an enema to clean the system. (Gender non-conforming, 22 yo, South Africa)

In contrast, a majority of participants in the US (74%), Peru (65.7%) and Thailand (90.6%) had previously used a rectal douche before RAS (See Table 4). Participants in the US (84%) and Peru (63%) most commonly used a bulb douche applicator, and many participants who had douched prior to this study reported that the study douche was similar, if not identical, to the one they regularly use. This provided an extra level of convenience when fitting the study douche into their routines, as expressed by one participant:

It's something that I already use. Um, so it had like a dual function of me participating in the study and also just being a part of my general bottoming routine. (Cisgender man, 21 yo, Pittsburgh)

However, in Thailand, a hose applicator was most often used (82%), described as connected to a bidet, so the applicator provided for the study was not as familiar.

Impact of Prior Douche Use on Preference

Based on Fisher's Exact Test, participants who had prior experience using rectal douches were significantly more likely ($p=0.03$) to select the douche as their most preferred product. (See Table 5). For many, it was a behaviorally congruent habit they did not have to modify:

Even if it wasn't the enema, the study product, I would douche every time I'd [have RAS], so. Like it's just something I did...it's something that brought zero change to my regular routine...it's natural, it feels like shaving to me. (Gender non-conforming, 21 yo, Pittsburgh)

Another participant in Peru mentioned being used to the process of douching, but found that the study douche bottles were preferable to what he had been using:

I just always used rectal douches, that's it. In the pharmacy they sell a product to do enemas and a bottle that you press for the water. It's similar but a different version...the one from the study is much more accessible and easier. (Cisgender man, 26 yo, Peru)

Rectal Suppository

Preference for Suppository by Country

The suppository was preferred by most from Malawi (59.1%). In contrast, only a small minority of participants from other countries reported preferring the suppository (US: 18.9%, Peru 21.1%, Thailand 16.7%, and South Africa 6.9%). (See Table 3). Based on participant interviews, the small, portable format of the suppository made it very discreet, which was critical in a context such as Malawi where same sex behavior is criminalized and being seen with a product that can be linked to anal sex could put people at risk socially and legally. A few people made reference to this in the Final Interview:

It's portable that one can carry it around or just put in the pocket. It's not easy for somebody to recognize it and if dropped one would think that it is some medicine. (Cisgender man, 31 yo, Malawi)

I didn't like the douche because it was difficult to use and it was a challenge to store the bottle, unlike the suppository. The suppository can easily be stored or carried without anyone recognizing what it is, while with the douche one can be questioned by others about it, so I didn't like it much. (Transgender woman, 29 yo, Malawi)

Others liked that it could be used to facilitate sex in place of a lubricant:

It didn't take long to melt and after melting it would soften the rectum so that penetration was easy. (Cisgender man, 31 yo, Malawi)

In contrast, in the US, Thailand and South Africa, where the suppository was the least preferred product, participants cited various reasons. In the US, most notably participants disliked its large size, greasy/oily feel, and that it dissolved too slowly:

It was really big, so I just felt it a lot longer and it took longer to dissolve. When it did dissolve, it felt like I had lube down there. (Cisgender man, 26 yo, San Francisco).

Participants in Thailand also mentioned the greasy/oily texture, large size and feeling that it leaked out:

Table 5 Product preference by history of product use

	Preferred product: douche (selection of preferred product, BEST)			Preferred product: suppository (selection of preferred product, BEST)			Preferred product: insert (selection of preferred study product, BEST)		
	No (n = 98)	Yes (n = 93)	P value	No (n = 149)	Yes (n = 41)	P value	No (n = 134)	Yes (n = 58)	P value
History of product use									
Ever used douche (n = 127)	58 (45.7%)	69 (54.3%)	0.03	103 (81.1%)	24 (19.0%)	0.26	93 (72.7%)	35 (27.3%)	0.25
Never used douche (n = 64)	40 (62.5%)	24 (37.5%)		46 (73.0%)	17 (27.0%)		41 (64.1%)	23 (35.9%)	
Ever used sup-pository (n = 7)	2 (28.57%)	5 (71.4%)	0.27	5 (71.4%)	2 (28.6%)	0.65	7 (100%)	0 (0)	0.10
Never used sup-pository (n = 184)	96 (52.2%)	88 (47.8%)		144 (78.7%)	39 (21.3%)		127 (68.7%)	58 (31.4%)	
Ever used insert (n = 9)	3 (33.3%)	6 (66.7%)	0.32	8 (88.9%)	1 (11.1)	0.69	7 (77.8%)	2 (22.2%)	0.3
Never used insert (n = 181)	95 (52.5%)	86 (47.5%)		140 (77.8%)	40 (22.2%)		126 (69.2%)	56 (30.8%)	

Bold value indicates statistically significant

The product size was big. It also needs to be used with lubricant so that it can go inside the rectum...during sex there was some liquid from the melted product that came out, which caused some interruption. (Transgender woman, 26 yo, Thailand).

In South Africa, participants who liked the suppository least most often cited side effects, such as bloating/gas/the urge to evacuate, as the reason.

Prior Suppository Use by Country

Few participants in any country had ever used a suppository before RAS (See Table 4). Most participants who reported past suppository use had to use it for medical reasons unrelated to sex. Some participants had used a suppository as a laxative. One shared that:

The only time I've used a suppository was when I was in a motorcycle accident like ten years ago and um and the medication I was taking at the hospital would constipate me, so I needed a suppository. (Transgender woman, 30 yo, San Francisco)

Eight others specified that the medication delivered via suppository was for hemorrhoid treatment, and one indicated that they received a vitamin via suppository. Only one participant in Peru described using suppositories "to be more lubricated." (Cisgender man, 23 yo, Peru)

Rectal Insert

Preference for Insert by Country

The insert was the most preferred product by half of participants from Thailand (50%) and nearly half of those from South Africa (47%). In contrast, very few from Malawi (8.7%) and a minority from the U (25.6%) and Peru (21.1%) preferred the insert (See Table 3). Among participants in Thailand, the insert was preferred because it was easy to use, small and portable:

The one I like the most is the insert. Its first advantage is small size. It is smaller than the other products. It also came in a pill bottle which was portable and easy to store. The second point is the insert was easy to use...I just used my finger to push the product inside my anus one to two inches...it dissolved faster than the suppository. (Transgender woman, 26 yo, Thailand).

Also, one person mentioned that, in contrast to the suppository, the insert held up well to the heat:

It didn't require a low temperature. I could store it anywhere. I could also bring it outside...I don't have to be

too concerned about it melting or breaking. (Cisgender man, 21 yo, Thailand).

In South Africa, participants who preferred the insert gave similar reasons of ease of use ($n=3$) small size and portability:

It's tiny enough that I can tuck it away easily and I can just put it in a small container when I'm traveling. (Gender non-conforming, 22 yo, South Africa)

On the other hand, in Malawi and Peru, the insert was the least preferred product. Based on interviews, participants in Malawi disliked its small size, felt they needed lubricant to apply it and reported side effects, such as pain bloating, gas or the urge to evacuate. Those in Peru disliked the rough, scratchy texture which led to irritation and discomfort.

Prior Insert Use by Country

In Malawi and South Africa, a handful had ever used a rectal insert, described in the survey as "any object other than a suppository that you may have inserted in your rectum or butt to clean it," prior to RAS, and only one of the participants selected for a Final Interview had used an insert prior to the study. This same participant shared that they had previous experience with all study products, including the suppository and the douche (See Table 4).

Discussion

While overall, acceptability was high across product types in the MTN-035 study [22], preference varied by country and history of similar product use. Rectal microbicide acceptability could be contingent on a variety of factors that go beyond typical measures such as ease of use or liking the way the product feels. For example, participants who had already established douching as a habit before RAS were more likely to prefer the douche as a RM over less familiar products like the suppository or insert, as they found it behaviorally congruent; that is, they were already douching prior to RAS and the addition of a medicated douche for HIV prevention would be easy to incorporate into their regular behavior.

However, for those who live in areas where homosexuality, transgender identity, and anal sex are strongly stigmatized or who live with others who are unaware of their sexuality, a discreet product that is easy to store and carry may be more important for product preference. This could also be a critical factor for consideration in future product use, as purchasing a product that is more obviously designed for use prior to RAS or associated with same-sex behaviors could be a concern for those who fear stigma

or discrimination, as evidenced by barriers to oral PrEP uptake around the world [25–28]. Additionally, environmental factors such as living in a hot climate could impact perceived product stability. For example, participants in Thailand mentioned that the insert appeared more stable in higher temperatures as compared to the suppository.

Based on participant feedback, each product delivery form had positive attributes. Whether due to the ease and convenience of the dosage forms themselves (described as quick, easy, small, portable, smooth, discreet) or the feeling after using the product (lack of side effects, clean, lubricated), participants in all countries found distinct advantages to each. These findings support continued development of a variety of RM dosage forms and formulations, as this study is one of few empirical studies in which participants used and compared different dosage modalities, as opposed to measures of hypothetical acceptability or acceptability of a drug-containing product that could have different side effects beyond the dosage form. A similar study of vaginal microbicide formulations had comparable findings, in that product preference varied within and across countries, indicating the need for a range of options for end-user [29]. Future research could expand on these findings by asking participants in different countries to brainstorm their ideal topical microbicide product, and to identify the most important factors for consistent product use in their particular context.

Our study had several limitations. First, acceptability was measured by self-report via CASI and IDIs; therefore, respondent bias may have impacted participants' reports. Some participants were recruited from lists of prior research participants at study sites, and therefore may have been more familiar with rectal microbicides than the average person and not be representative of the population at risk for HIV. However, sites did not recruit participants with prior experience in studies of rectal products. In addition, participants were testing placebo product delivery methods, so any potential drug-related side effects that could impact acceptability would not be detected in this study. Finally, product use instructions for each product were developed with the goal of ensuring that an effective product would have time to be absorbed prior to RAS. As such, participants were instructed to use the products no more than 3 h beforehand, which may not reflect typical use of products such as rectal douches and could have impacted acceptability due to portability.

In conclusion, this study demonstrates that experience using a product successfully in the past, country-specific practices prior to RAS, privacy concerns in areas where discrimination toward same-sex and transgender sexual contact is common, and even the geographic climate can impact product acceptability. Our findings support the argument that

there is no “one size fits all” solution for PrEP use, and that having access to a range of acceptable products available is the best way to increase use and strengthen HIV prevention programs globally. Understanding nuances in product preferences is essential to developing products that can be easily adopted by intended users worldwide.

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Declarations

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