# SOCIAL HARMS IN FEMALE-INITIATED HIV PREVENTION METHOD RESEARCH: STATE OF THE EVIDENCE

**Elizabeth T. Montgomery**[1], **Sarah T. Roberts**[1], **Annalene Nel**[2], **Mariette Malherbe**[2], **Kristine Torjesen**[3], **Katherine Bunge**[4], **Devika Singh**[4], **Jared M. Baeten**[5], **Jeanne Marrazzo**[6], **Z. Michael Chirenje**[7], **Samuel Kabwigu**[8], **Richard Beigi**[4], **Sharon A. Riddler**[4], **Zakir Gafoor**[9], **Krishnaveni Reddy**[10], **Leila E Mansoor**[11], **Lulu Nair**[11], **Kusbashini Woeber**[9], **Jothi Moodley**[9], **Nitesha Jeenarain**[9], **Samantha Siva**[9], **Logashvari Naidoo**[9], **Vaneshree Govender**[9], **Thesla Palanee-Phillips**[10]

[1]Women's Global Health Imperative, RTI International, San Francisco, CA [2]International Partnership for Microbicides (IPM), Paarl, South Africa [3]FHI 360, Durham, NC [4]University of Pittsburgh, Pittsburgh, PA [5]University of Washington, Seattle, WA [6]University of Alabama, Birmingham, AL [7]University of Zimbabwe, Harare, Zimbabwe [8]Makerere University, Kampala, Uganda [9]HIV Prevention Research Unit, Medical Research Council of South Africa, Durban, South Africa [10]Wits Reproductive Health and HIV Institute, Johannesburg, South Africa [11]Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa

## Abstract

**Objectives:** Assessment of safety is an integral part of real-time monitoring in clinical trials. In HIV prevention research, safety of investigational products and trial participation has been expanded to include monitoring for "social harms" (SH), generally defined as negative consequences of trial participation that may manifest in social, psychological, or physical ways. Further research on SH within HIV prevention research is needed to understand the potential safety risks for women and advance the implementation of prevention methods in real-world contexts.

**Methods:** Secondary analysis of quantitative data from three randomized, double-blind, placebo-controlled trials of microbicide candidates in sub-Saharan Africa was conducted. Additionally, we assessed data from two prospective cohort studies that included participants who became HIV-positive or pregnant during parent trials.

**Results:** SH reporting was low across the largest and most recent microbicide studies. SH incidence per 100 person-years ranged from 1.10 (95% CI: 0.78-1.52) to 3.25 (95% CI: 2.83-3.74) in the phased trials. Reporting differed by dosing mechanism (e.g. vaginal gel, oral tablet, ring) and study, most likely as a function of measurement differences. SH were most frequently associated with male partners, rather than, for example, experiences of stigma in the community.

**Conclusions:** Measurement and screening for SH is an important component of conducting ethical research of novel HIV prevention methods. To date SH incidence reported in microbicide trials has been relatively low (<4% per 100py), and the majority have been partner-related events. However, any incidence of SH within the context of HIV prevention is important to capture and

understand for the safety of individual women, and for the successful impact of prevention methods in a real-world context.

## Background.

Assessment of safety is an integral part of real-time monitoring in clinical trials. In HIV prevention research, safety monitoring has been expanded to include "social harms", generally defined as negative consequences of trial participation, that may manifest in social, psychological, or physical ways.[1] Participants may face social harms (SH) for being at risk of HIV, being perceived to have HIV, or for participating in research. A variety of factors, including cultural norms around sexuality and morality, local understandings of gender roles, previous experience of violence within intimate partner relationships, and stigma contribute to and exacerbate SH risk.[2–4]

The concept of SH in HIV prevention research was introduced in relation to vaccine studies in 1998,[5] and much of the research on SH stems from these early HIV prevention studies. Little has been published about the frequency of SH experienced during microbicide or oral pre-exposure prophylaxis (PrEP) studies. Although developed as biomedical technologies to provide women with agency to protect themselves from HIV, research has indicated that men's attitudes toward products influence women's acceptability and use.[6–8] Emerging evidence also suggests that microbicides in gel or ring formulations, or oral PrEP, may exacerbate women's risk for SH, including intimate partner violence (IPV).[9,10] Experience of SH may also inhibit women's ability to consistently use HIV prevention products.[9,11]

As more HIV prevention products are available, a greater number of women may be placed at risk of experiencing SH. It is important to monitor whether, when and how prevention methods exacerbate experiences of SH in a trial context, so as to mitigate risk and potential negative impact on product uptake and use. In this paper we review how SH have been assessed in HIV prevention studies, report on their frequencies, and discuss best practices for monitoring and addressing SH in future research and programmatic work.

## METHODS

### Study design and sample.

We conducted a secondary analysis of SH data from three randomized, double-blind, placebo-controlled phase IIb and phase III trials of microbicide candidates in sub-Saharan Africa, two of which were sponsored by the Microbicide Trials Network (MTN) and one by the International Partnership of Microbicides (IPM). The purpose of this analysis was to understand how the largest and most current multisite microbicide trials with women were defining and measuring SH, and to assess the frequency and scope of reported SH.

Data included in this analysis were drawn from a convenience sample of studies from which colleagues and collaborators provided permission to access protocol-specified SH procedures and data. Although not intended as a comprehensive review, all recent (post 2010) phase IIb and III microbicide candidate trials of which we had knowledge were

invited to participate, and all but one were able to provide data at the time of request. Studies are summarized in Box 1.

### Study Settings.

All trials were conducted with women in sub-Saharan Africa. The VOICE and ASPIRE studies had sites in Uganda (Kampala); Zimbabwe (Chitungwiza, Harare); Malawi (Blantyre, Lilongwe) and South Africa (Cape Town, Durban, Johannesburg, Klerksdorp, Soweto). The Ring Study was conducted in Uganda (Masaka) and South Africa (Brits, Cape Town, Edendale, Ladysmith, Limpopo, Pinetown). The MTN-015 and MTN-016 cohort studies include data from global MTN sites, but only data from the aforementioned MTN sites were included in this analysis.

### Measures and procedures.

**<u>Trial-specific definition and measurement of social harms.:</u>** The definition of "social harm" and the process by which SH were measured differed across studies. In MTN studies, SH were defined as "non-medical adverse consequences experienced by participants as a result of their participation in the study." Examples of SH in MTN study-specific procedures manuals included difficulties in personal relationships with partners, family members, and friends, as well as stigma or discrimination because participants could become known as HIV-positive or at "high risk" for HIV infection.

In the VOICE Study[14] data about experiences of SH were systematically collected on Case Report Forms (CRF) from all participants as part of behavioral assessments administered by interviewers quarterly, at the product use end visit, and at the termination visit. SH data were captured in a two-tier system. First, participants were read structured questions about whether they had experienced any "problems" since the last visit as a result of being in this study and presented with a list of potential people including an open-ended "other" response. If any problems were reported, they were asked whether the problem resulted in emotional, physical, or economic harm, or harm to their children. Participants could also spontaneously report study-related issues and problems to staff at any visit.

The SH reporting policy for VOICE was revised for the ASPIRE Study[15]. Interviewers asked women a standardized question about SH quarterly and at the product use end visit: *"At any time during the past 3 months, have you experienced a social harm related to your study participation?"* Staff were permitted to clarify the language if it was not understood. SH reported through this structured mechanism, or through any spontaneous report, triggered the completion of a *Social Impact Log* CRF which captured a description of the event, the onset date, whether it involved physical harm to her or her children, and the impact on her quality of life (minimal disturbance, moderate disturbance with no significant impact, or major disturbance with significant impact). Each SH was characterized as being related to family, a sex partner, other personal relationships, travel/immigration, employment, education, medical/dental, housing, or other.

In the MTN-015 study,[17] a prospective cohort study for women who seroconverted on VOICE, ASPIRE or other MTN investigational drug-related studies, participants were asked,

similarly to VOICE, whether they had "any problems with the following people [list] as a result of being in the study" at their month 3 and 6 visits, and every 6 months thereafter including the final study visit. Questions were read from a questionnaire by a staff member. Participants were asked to specify the type of harm experienced. In this study, the traditional definition of SH as being "related to study participation" was expanded to measure harms related to being recently infected with HIV.

In the MTN-016 study,[18] a prospective cohort registry of women who became pregnant during trials of microbicide or oral PrEP products and their infants, participants were asked about experiences of SH at all follow-up visits, including quarterly during pregnancy; at pregnancy outcome; at 1, 6, and 12 months after birth; and at interim visits. MTN 016 study staff were instructed to "inquire about social harms" on visit checklists but did not administer structured questions to participants. If a SH was reported, a CRF was completedabout the SH, including whether it impacted the woman, the infant, or both;, whether problems with a list of people had occurred, and whether the problem resulted in emotional, physical, economic/financial, or harm to children.

The Ring Study defined SH as "an untoward event that causes physical, emotional or financial harm to a trial participant." SH were assessed and documented at every visit during HIV counseling sessions. In IPM study operating manuals SH were further defined as: *"social harm means literally a social interaction that has caused harm to the participant"*, which might encompass non trial-related harms. If SH were reported, a three-part CRF was completed. The first section included questions for the participant to establish the SH type , her opinion of its relatedness to trial participation and if the SH was resolved. The second section required the staff member to classify the harm as physical, emotional or financial, and to document any follow-up required. The third section was a follow-up form that documented any additional or new information to a previously reported SH.

**Analysis.:** For each of the studies we reviewed study protocols, procedural manuals and data collection forms to identify how SH were defined, measured, referred (if applicable) and reported to protocol teams and ethics committees. For the MTN studies, raw individual-level data were obtained from the MTN Statistical and Data Management Center (SCHARP) and analyzed in Stata. Incidence of overall SH (from any perpetrator) was computed as each participants' time from enrolment to reported onset of the first SH or end of study, and incidence of partner-related SH was computed time to first partner-related SH or end of study for each participant. Frequencies of SH type, perpetrator and outcome were tabulated. For IPM 027, computed statistics, using SAS®, were provided by ClinData, an IPM external service provider for biostatistics.

## RESULTS

### Frequency, perpetrators and types of social harms

In VOICE, 218 SH were reported by 195 women, representing an incidence of 3.25 (95%CI: 2.83 - 3.74) first SH events per 100 women-years (Table 1). The incidence of partner-related SH was 1.85 (95%CI: 1.53-2.22), with just over half (112, 51.4%) of reported SH being partner-related. The proportion of SH reported did not differ by arm assignment (tablet vs.

gel). The majority of SH (98%) were described as causing emotional harm, with a smaller number, in addition to causing emotional harm, reported as causing economic harm (12%) or harm to children (2%). Eleven SH (5%) were reported to cause physical harm (Table 2). The majority of SH experienced by participants in the gel arm resulted from misconceptions about the study as well as a disapproval of physical effects of the gel that affected intercourse, such as vaginal wetness. Outcomes varied from general disapproval, forced removal from the study, to incidences of sexual violence. The majority of SH in the tablet arm were perpetrated by male partners, most frequently because of misconceptions about the study (e.g., partners believed their female partners were participating because they were HIV positive). Accusations, judgment or shaming around HIV status by friends, colleagues, and community members were also frequently reported by those in the tablet arms.

During ASPIRE, 91 participants reported 94 SH events, representing an incidence of 2.00 per 100 women-years (95%CI: 1.63-2.46; Table 1).[9] Eighty-five women reported partner-related SH during the study, including two women who reported two SH each (incidence of first partner-related event: 1.87, 95% CI: 1.51 - 2.31). These comprised 92.6% of all SH reported during the study. Twenty-six (28.9%) SH resulted in physical harm to the participant; there were no reports of harm to the participant's children. The majority of partner-related SH were reported to have minimal impact on quality of life (51 SH or 58.6%), with 27 (31.0%) classified as moderate disturbance and 9 (10.4%) causing a major disturbance with significant impact. Those with major impact were often related to the participant's partner threatening divorce or separation or no longer wanting to have sex with the participant if she did not leave the study. Participants also reported physical violence from male partners when the ring was discovered during sex and relationship dissolution after partner notification for STI treatment (data not shown). At the end of the study, seven SH were unresolved or unable to be resolved (n=4) due to participants being lost to follow-up.

In the IPM Ring Study, 37 participants reported 39 SH events, representing an incidence of 1.10 per 100 women-years (95%CI: 0.78-1.52). Thirty-two women reported 34 partner-related SH during the study, with an incidence of 0.95 per 100 women years (95%CI: 0.65-1.34). The majority (33; 85%) of SH were reported as emotional harm to the participant and 14 (36%) SH resulted in physical harm. Two (5%) participants reported harm to others including children and family members. The perpetrators included the sex partner for 34 (87%) of the participants, family members for three (8%), co-workers in one (3%) and a stranger in one (3%) participant. Partner-related SH were mostly reported as a minor disturbance (15 SH; 38%), with 13 (33%) classified as a moderate disturbance and 10 (26%) causing a major disturbance.

In the MTN-015 study, nine participants (2.3%) reported partner-related SH associated with being HIV-positive; and one (0.3%) reported partner-related SH associated with study participation (Table 2). The SH from study participation was due to the partner complaining about her absence from home during study visits. The majority of harms related to the participants' HIV status were emotional and occurred when the relationship dissolved or anger and blame over who infected whom within the partnership. There were also several

reports of withdrawal of financial support after the participant's HIV status disclosure, and one report of physical violence.

In the MTN-016 study, one SH was reported (data not shown), and it was an emotional harm associated with the male-partner. The participant reported her husband did not believe she was planning to attend an ultrasound appointment, but thought she was going to meet another man. The participant completed the appointment and the partner did not accompany her.

## DISCUSSION

Monitoring of SH in HIV prevention research is an important strategy to assess and address adverse consequences of study participation or product use that go beyond clinical adverse events (AEs). Unlike AEs, "social harms" are not clearly defined or recognized by an international regulatory body, and in microbicide and other HIV prevention studies, their measurement and definition (and recognition of the importance thereof) has evolved over the past two decades. While numerous HIV prevention studies have noted the importance of understanding and mitigating SH related to study participation, few studies have conducted in-depth explorations of SH, including how SH might differ by dosing platform (e.g. vaginal gel, oral tablet, vaginal ring); and few have explored the incidence of SH in the African context.[1,4,10,19–22] In this analysis of secondary data we identified several key findings. First, SH reporting was low across the largest and most recent microbicide studies.[23] Second, reporting differed by dosing mechanism and study, most likely as a function of measurement differences. Third, SH were most frequently associated with male partners.

Although no benchmarks exist, the included studies reported a low rate of SH among a small proportion of participating women, and when measured, the majority of SH did not negatively impact quality of life (Table 2). When reported, many SH were acts of IPV, most commonly emotional IPV, but also physical. Given the high background rates of IPV in the region – the estimated lifetime IPV prevalence is 36.3% in Africa (95%CI: 32.7-40.5)[23], in juxtaposition to the relatively low rates of SH reported in these studies, several questions are raised, for example, *how are trial participants different than other women in their communities?* This is complex to measure, but it is likely that some women most vulnerable to SH and HIV are not willing or able to join prevention trials, and implementation scientists and public health practitioners should pre-emptively prepare for monitoring SH in prevention distribution programs. *Do trial participants under-report SH because they fear they will be exited from the trial or for other reasons?* In most cases participants would not be exited and are told this during consent processes and counseling. However, qualitative studies have shown participants may report socially desirable behaviors about product adherence (i.e. do not report non-use) so as not to be removed from the study.[24,25] Thus it's likely some participants are fearful of reporting experiences that might jeopardize trial participation.

The overall incidence of SH associated with participating in the dapivirine ring trials (ASPIRE and The Ring Study) was lower than what was reported in the tablet or gel arms of VOICE. However, the proportion of SH that were *partner-related* in both ring trials was

higher than in tablet or gel studies and the incidence of partner-related SH was similar across all dosing platforms. Most SH to date in HIV prevention trials have been partner-related problems associated with a study participant using an HIV-related or vaginal product, and the perceived implications of this on promiscuity, trust or HIV-status.[9] These findings are consistent with previous reports about the importance of male partners on women's microbicide use.[24,26–28]

Importantly, it is unknown whether the partner-related differences between these studies are meaningful or a consequence of measurement. In studies such as ASPIRE and The Ring Study, SH were monitored systematically at every visit, and analogous to AEs, a more in-depth description of events (e.g. onset, duration, severity) were recorded. In ASPIRE, SH reporting was triggered by overtly asking participants if they had experienced a SH, or by participants spontaneously describing an event that was then recorded. It is unknown how well, or how consistently, participants understood the meaning of "social harm" when asked this question, which may have introduced a classification bias. During The Ring Study, counselors assessed experiences of SH during every HIV counseling visit, thus there was a less standardized and systematic application of a structured question. In others, like VOICE, participants were asked a more general question about experiencing "problems" with different people in their lives, followed by detailed questioning to determine if a SH had occurred. While the use of a general term like "problems" can also be subject to classification errors, it may be an effective screening question to explore potential SH in more depth. Perhaps the best assessment of SH in future studies would include a hybrid approach: enquiring about problems with various types of people (family, friends, partner, etc.) at every visit, then probing about, and documenting, SH through counseling discussions and structured questionnaires. Additionally, data capture regarding the disturbance of SH, and impact on quality of life will provide important contextual information about each event.

Additional important questions raised through this analysis are: *Do participants see SH as everyday life experiences rather than SH? Does the definition of SH used by researchers adequately address the experiences of harm and violence in women's lives?* Many harms may exist in women's lives, and with the exception of The IPM Ring Study and MTN-015, these would not get classified as SH if they were not "study-related". Further, it may be difficult for women and researchers to know if an event is truly "study-related", as the causal relationship is not always clear, particularly in abusive or controlling relationships. In MTN-015, SH were categorized as "definitely" or "possibly" study-related, and in The Ring Study they were classified as "study-related" or "not study-related", which helps to acknowledge this ambiguity. Future projects may consider documenting all SH and subsequently quantifying, as with standard AE practice, the relatedness of SH to the intervention. Integration of tools to measure and respond to IPV within the context of HIV prevention trials and demonstration projects may also expand beyond the study-related definition of SH and better address women's needs. For example, addressing IPV/SH could improve adherence and study outcomes, a hypothesis that several projects have aimed or are seeking to test.[29–31] However, addressing IPV is no small feat: it requires substantial time and resources in often over-burdened settings. There is a need for short, validated tools to measure IPV in prevention trial or public health clinics, as compared to longer questionnaires used in violence-related studies (e.g. Violence Against Women Scale

(VAWS).[23,32,33] Self-administered and/or electronic-based tools may also help address human resource constraints and potential underreporting of SH.

Although anticipated to be a source of SH, community-based stigmatization SH were seldom reported in these trials. This may be reflective of a trend towards wider acceptance and knowledge of HIV in communities with significant research taking place. It may also reflect upon research groups' efforts to engage with Community Advisory Boards, and their sensitization activities in research catchment areas. Indeed, Volk et al. reported the extensive community outreach they conducted prior to an HIV vaccine trial in South Africa may have reduced SH in their study.[19] A number of opinion papers and guideline documents, including those on Good Participatory Practice,[34] have argued that introductory presentations to local communities will create a better understanding of their research perceptions, and have a positive impact on the uptake and acceptability of investigational products.[2,35]

Tarimo et al. argue it is vital to follow up with participants after they have completed a trial because some will continue to suffer from SH post-trial, and these harms may be different than those experienced during the study.[22] To our knowledge this has not been done and might offer important information for the research community. There is also increased recognition that investigation into SH should be counter-balanced with measurement of social benefits such as enhanced confidence, counseling support, or HIV prevention and health screening. This is being formalized in some protocols, like the MTN-025/HOPE Open Label Extension study of the dapivirine ring.

There are several limitations of this analysis. First, a systematic review was not feasible due to paucity of published SH data, and the included studies represent the majority, but not all, recent microbicide trials, therefore results should not be considered comprehensive. These data were captured from trial participants who may be inherently different from other women in important ways, including their risk for SH. Underreporting of SH was likely to have occurred due to participant fear of being exited from these studies, because a SH was not remembered, was perceived as "normal" behavior, or for other measurement-related reasons, thus the true "accuracy" of our estimates is not known. While these data and approaches could inform future assessments of barriers to PrEP uptake in women, it is also unknown how the frequency and type of SH reported in these studies will extend to real-world contexts and other HIV approaches.

In conclusion, measurement of and screening for SH is an important component of conducting ethical research on novel HIV prevention methods. To date, SH incidence reported in microbicide trials has been relatively low (<4% per 100py), and the majority have been partner-related events, rather than experiences of stigma in the community. To gain a more comprehensive understanding of the context in which novel HIV prevention methods are integrated into women's lives, future research should screen more widely for SH, social benefits, and experiences of partner-related and non-partner-related violence. SH are important to capture and understand for the safety of women and the successful impact of prevention methods in real-world contexts.

# REFERENCES

1. Milford C, Barsdorf N, Kafaar Z. What should South African HIV vaccine trials do about social harms? AIDS Care 2007; 19(9): 1110–7. [PubMed: 18058395]

2. Woodsong C, Karim QA. A model designed to enhance informed consent: experiences from the HIV prevention trials network. Am J Public Health 2005; 95(3): 412–9. [PubMed: 15727968]

3. Haire BG. Preexposure prophylaxis-related stigma: strategies to improve uptake and adherence - a narrative review. HIV/AIDS (Auckland, NZ) 2015; 7: 241–9.

4. Saethre E, Stadler J. Malicious Whites, Greedy Women, and Virtuous Volunteers. Medical anthropology quarterly 2013; 27(1): 103–20. [PubMed: 23674325]

5. Sheon A, Wagner L, McElrath J, et al. Preventing discrimination against volunteers in prophylactic HIV vaccine trials: lessons from a phase II trial. JAIDS 1998; 19: 519–26. [PubMed: 9859967]

6. Lanham M, Wilcher R, Montgomery ET, et al. Engaging male partners in women's microbicide use: evidence from clinical trials and implications for future research and microbicide introduction. J Int AIDS Soc 2014; 17(3 Suppl 2): 19159. [PubMed: 25224618]

7. Montgomery ET, van der Straten A, Chidanyika A, Chipato T, Jaffar S, Padian N. The importance of male partner involvement for women's acceptability and adherence to female-initiated HIV prevention methods in Zimbabwe. AIDS and behavior, 2010 http://www.springerlink.com/content/y88454311504j172/ (accessed Sep 16).

8. Montgomery ET, Stadler J, Hartmann M, et al. Male partner roles and influence on women's use of HIV pre-exposure prophylaxis in Johannesburg AIDS Impact; 2013 Sept 29-Oct 3, 2013; Barcelona, Spain; 2013.

9. Palanee-Phillips T, Roberts ST, Reddy K, et al. Impact of partner-related social harms on women's adherence to the dapivirine vaginal ring during a phase III trial. Journal of acquired immune deficiency syndromes (1999) 2018.

10. Stadler J, Delany-Moretlwe S, Palanee T, Rees H. Hidden harms: Women's narratives of intimate partner violence in a microbicide trial, South Africa. Social Science & Medicine 2014; 110: 49–55. [PubMed: 24721447]

11. Roberts ST, Haberer J, Celum C, et al. Intimate Partner Violence and Adherence to HIV Pre-exposure Prophylaxis (PrEP) in African Women in HIV Serodiscordant Relationships: A Prospective Cohort Study. Journal of acquired immune deficiency syndromes (1999) 2016; 73(3): 313–22. [PubMed: 27243900]

12. Delany-Moretlwe S, Lombard C, Baron D, et al. Tenofovir 1% vaginal gel for prevention of HIV-1 infection in women in South Africa (FACTS-001): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Infectious diseases 2018; 18(11): 1241–50. [PubMed: 30507409]

13. Rees H, Delany-Morelwe S, Lombard C. FACTS 001 phase III trial of pericoital tenofovir 1% gel for HIV prevention in women. Conference on Retroviruses and Opportunistic Infections (CROI); 2015; 2015 p. 23–6.

14. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. New England Journal of Medicine 2015; 372(6): 509–18. [PubMed: 25651245]

15. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. The New England journal of medicine 2016.

16. Nel A, van Niekerk N, Kapiga S, et al. Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women. New England Journal of Medicine 2016; 375(22): 2133–43. [PubMed: 27959766]

17. Riddler SA, Husnik M, Gorbach PM, et al. Long-term follow-up of HIV seroconverters in microbicide trials - rationale, study design, and challenges in MTN-015. HIV clinical trials 2016; 17(5): 204–11. [PubMed: 27465646]

18. Mhlanga FG, Noguchi L, Balkus JE, et al. Implementation of a prospective pregnancy registry for antiretroviral based HIV prevention trials. HIV clinical trials 2018; 19(1): 8–14. [PubMed: 29268654]

19. Volk JE, Hessol NA, Gray GE, et al. The HVTN503/Phambili HIV vaccine trial: a comparison of younger and older participants. International journal of STD & AIDS 2014; 25(5): 332–40. [PubMed: 24104693]

20. Thapinta D, Jenkins RA. Starting from scratch: program development and lessons learned from HIV vaccine trial counseling in Thailand. Contemporary clinical trials 2007; 28(4): 409–22. [PubMed: 17196444]

21. Essack Z, Slack C, Koen J, Gray G. HIV prevention responsibilities in HIV vaccine trials: complexities facing South African researchers. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 2010; 100(1): 45–8. [PubMed: 20429488]

22. Tarimo EA, Munseri P, Aboud S, Bakari M, Mhalu F, Sandstrom E. Experiences of social harm and changes in sexual practices among volunteers who had completed a phase I/II HIV vaccine trial employing HIV-1 DNA priming and HIV-1 MVA boosting in Dar es Salaam, Tanzania. PloS one 2014; 9(3): e90938. [PubMed: 24603848]

23. García-Moreno C, Pallitto C, Devries K, Stöckl H, Watts C, Abrahams N. Global and regional estimates of violence against women: prevalence and health effects of intimate partner violence and non-partner sexual violence: World Health Organization; 2013.

24. Montgomery ET, van der Straten A, Chitukuta M, et al. Acceptability and use of a dapivirine vaginal ring in a phase III trial. AIDS 2017; 31(8): 1159–67. [PubMed: 28441175]

25. van der Straten A, Montgomery ET, Musara P, et al. Disclosure of pharmacokinetic drug results to understand nonadherence. AIDS 2015; 29(16): 2161–71. [PubMed: 26544581]

26. Montgomery E, van der Straten A, Torjesen K. "Male involvement" in women and children's HIV prevention: challenges in definition and interpretation. J Acquir Immune Defic Syndr 2011; 57(5): e114. [PubMed: 21860358]

27. Montgomery ET, van der Straten A, Chidanyika A, Chipato T, Jaffar S, Padian N. The importance of male partner involvement for women's acceptability and adherence to female-initiated HIV prevention methods in Zimbabwe. AIDS Behav 2011; 15(5): 959–69. [PubMed: 20844946]

28. Montgomery ET, van der Straten A, Stadler J, et al. Male partner influence on women's HIV prevention trial participation and use of pre-exposure prophylaxis: the importance of "understanding". AIDS Behav 2015; 19(5): 784–93. [PubMed: 25416076]

29. Cowan FM, Delany-Moretlwe S, Sanders EJ, et al. PrEP implementation research in Africa: what is new? Journal of the International AIDS Society 2016; 19: 21101. [PubMed: 27760680]

30. WOMEN'S RISK O. Generating CHARISMA: development of an intervention to help women build agency and safety in their relationships while using HIV prevention methods.

31. Settergren SK, Mujaya S, Rida W, et al. Cluster randomized trial of comprehensive gender-based violence programming delivered through the HIV/AIDS program platform in Mbeya Region, Tanzania: Tathmini GBV study. PloS one 2018; 13(12): e0206074. [PubMed: 30521530]

32. Schraiber LB, Latorre MdRDO, França I Jr, Segri NJ, d'Oliveira AFPL. Validity of the WHO VAW study instrument for estimating gender-based violence against women. Rev Saude Publica 2010; 44(4): 658–66. [PubMed: 20676557]

33. Nybergh L, Taft C, Krantz G. Psychometric properties of the WHO Violence Against Women instrument in a female population-based sample in Sweden: a cross-sectional survey. BMJ open 2013; 3(5): e002053.

34. Good participatory practice guidelines for biomedical HIV prevention trials. Retrieved from 2011. http://www.avac.org/sites/default/files/resource-files/Good%20Participatory%20Practice%20guidelines_June_2011.pdf.

35. Ethical issues in the NIMH Collaborative HIV/STD Prevention Trial. AIDS 2007; 21 Suppl 2: S69–80. [PubMed: 17413266]

36. Riddler SA, Husnik M, Gorbach PM, et al. Long-term follow-up of HIV seroconverters in microbicide trials - rationale, study design, and challenges in MTN-015. HIV clinical trials 2016: 1–8. [PubMed: 26899538]

**Box 1.**

## Summary of Microbicide Trials included in this analysis

| Name | Study design | N | Location | Duration |
|------|-------------|---|----------|----------|
| **IPM 027 /The Ring Study**[16] | Phase III randomized, placebo-controlled trial of the safety and effectiveness of the dapivirine vaginal ring | 1,959 | South Africa Uganda | 2012-2016 |
| **MTN-003/ VOICE**[14] Vaginal and Oral Interventions to Control the Epidemic | Phase IIb randomized, placebo-controlled trial to assess the safety and effectiveness of daily use of an antiretroviral (ARV) tablet (tenofovir or Truvada) or daily use of a vaginal gel (tenofovir gel) | 5,029 | South Africa, Uganda, Zimbabwe | 2009 -2012 |
| **MTN-015**[17] | Multi-site, prospective, observational cohort study of women following HIV-1 seroconversion in microbicide trials of ARV-based microbicides or oral pre-exposure prophylaxis (PrEP). | 409 | Malawi, South Africa, Uganda, Zimbabwe | 2009 - 2016 |
| **MTN-016/ EMBRACE**[18] Evaluation of Maternal and Baby Outcome Registry After Chemo-prophylactic Exposure | Prospective observational cohort study of maternal exposures to investigational HIV prevention agents. | 550 | Malawi, South Africa, Uganda, Zimbabwe | 2010-2015 |
| **MTN-020/ ASPIRE**[15] A Study to Prevent Infection with a Ring for Extended Use | Phase III randomized, placebo-controlled safety and effectiveness trial of a vaginal ring containing the antiretroviral dapivirine. | 2,629 | Malawi, South Africa, Uganda, Zimbabwe | 2012 -2015 |

**Table 1.**

Frequency and Incidence of Social Harms Reported in Microbicide Studies

| Study | N[*] | Women reporting SH | SH reported | Person-Years (py) | SH incidence per 100py | Partner-related SH[**] (%/SH) | Partner-related SH incidence per 100py[**] |
|---|---|---|---|---|---|---|---|
| **IPM 027/ The Ring Study**[16] | 1958 | 37 | 39 | 3359.09 | | 34 (87.2%) | 0.95 (95%CI: 0.65-1.34) |
| **MTN-003/ VOICE**[14] | 4943 | 195 | 218 | 5992.75 | 3.25 (95% CI: 2.83-3.74) | 112 (51.4%) | 1.85 (95%CI: 1.53-2.22) |
| *Tablet* | 2963 | 113 | 125 | 3729.51 | 3.03 (95% CI: 2.52 – 3.64) | 65 (52.0%) | 1.72 (95% CI: 1.35 – 2.19) |
| *Gel* | 1980 | 82 | 93 | 2263.24 | 3.62 (95% CI: 2.92-4.50) | 47 (50.5%) | 2.05 (95% CI: 1.54 – 2.73) |
| **MTN-015**[36] | 400 | 2 | 2 | 1183.96 | 0.17 (95%CI: 0.04-0.68) | 1 (50.0%) | 0.08 (0.01 – 0.60) |
| *HIV-related* | 400 | 12 | 13 | 1160.37 | 1.29 (95%CI: 0.78-2.14) | 11 (84.6%) | 0.94 (0.52 – 1.71) |
| **MTN-020/ ASPIRE**[15] | 2622 | 91 | 94 | 4548.34 | 2.00 (95%CI: 1.63-2.46) | 87 (92.6%) | 1.87 (95% CI:1.51 – 2.31) |

[*] Analysis sample size

[**] Partner-related py at risk is slightly higher because the py includes only time to the first partner-related SH.

**Table 2:**

Social harm classifications, perpetrators and outcomes, by study

| | VOICE | | ASPIRE | MTN 015 | | MTN 016 | IPM 027 |
|---|---|---|---|---|---|---|---|
| | Gel | Tablet | | Study-related | HIV-related | | |
| Number of "problems" reported[1] (n) | 168 | 225 | NA | 8 | 22 | 1 | NA |
| Unique participants reporting a "problem"[1] (n) | 138 | 201 | NA[2] | 8 | 20 | 1 | NA |
| Number of SH reported (n) | 93 | 125 | 94 | 2 | 16 | 1 | 39 |
| Unique participants reporting SH or experiencing SH from a reported problem[1] (n) | 82 | 113 | 91 | 2 | 15 | 1 | 37 |
| *Classification of harm experienced*[3]*: n (%)* | | | | | | | |
| Emotional | 91 (98) | 122 (98) | NA | 2 (100) | 16 (100) | 1 (100) | 33 (85) |
| Physical harm | 3 (3) | 8 (6) | 26 (28) | 0 | 2 (1) | 0 | 14 (36) |
| Economic harm | 15 (16) | 12 (70) | NA | 0 | 4 (3) | 0 | 7 (18) |
| Harm to children | 2 (2) | 2 (2) | 1 (1) | 0 | 4 (3) | 0 | 2 (5)[4] |
| *Perpetrator or source of problem/SH*[5]*: n (%)* | | | | | | | |
| Partner | 53 (60) | 70 (61) | 87 (93) | 1 (50) | 11 (69) | 1 (100) | 34 (87) |
| Family/ people at home (not partner) | 11 (13) | 18 (16) | 2 (2) | 0 | 1 (6) | 0 | 3 (8) |
| Friend/ personal relationships | 8 (9) | 8 (7) | 1 (1) | 1 (50) | 2 (13) | 0 | 0 |
| Employment-related/ co-workers | 9 (10) | 10 (8) | 2 (2) | 0 | 2 (13) | 0 | 1 (3) |
| Landlord or property owner | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 | NA |
| Health care provider or medical-related | 2 (2) | 5 (4) | 0 | 0 | 0 | 0 | 0 |
| Education-related | 1 (1) | 1 (1) | 0 | 0 | 0 | 0 | NA |
| Travel or Immigration-related | NA | NA | 0 | NA | NA | NA | NA |
| Church members | NA | NA | NA | NA | NA | NA | 0 |
| Community members known to you[6] | 3 (3) | 2 (2) | 1 (1) | 0 | NA | 0 | 0 |
| Strangers | NA | NA | NA | NA | NA | NA | 1 (3) |
| *Reported impact on quality of life* | | | | | | | |
| Minimal disturbance | NA | NA | 54 (57) | NA | NA | NA | 15 (38) |

| | VOICE | | ASPIRE | MTN 015 | | MTN 016 | IPM 027 |
|---|---|---|---|---|---|---|---|
| | Gel | Tablet | | Study-related | HIV-related | | |
| Moderate dist., no signif impact[7] | NA | NA | 29 (31) | NA | NA | NA | 13 (33) |
| Major disturbance w/ signif impact[7] | NA | NA | 11 (12) | NA | NA | NA | 10 (26) |

[1]VOICE, MTN 015 and MTN 016 were the only studies that systematically first asked about "problems" before probing further into experience of harms.

[2]"NA" in this table is used to indicate that the item was not measured

[3]SH could be classified in all categories that applied. The denominator in percentages is the total number of SH.

[4]Categorized as harm to others, including children

[5]For VOICE there are 16 of 218 SH for which the data are unclear as to the perpetrator. These have been excluded from these tabulations.

[6]In VOICE and ASPIRE these were captured under "other" and defined as community members or neighbors

[7]Significance of impact not captured on CRFs for The Ring Study