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State of the science of adherence in pre-exposure prophylaxis and microbicide trials

Felix M. Muchomba, MPH^{*}, Robin E. Gearing, PhD[†], Jane M. Simoni, PhD[‡], and Nabila El-Bassel, DSW^{*}

^{*}Global Health Research Center of Central Asia and the Social Intervention Group, School of Social Work, Columbia University, New York, NY

[†]Columbia University, New York, NY

[‡]Department of Psychology, University of Washington, Seattle, WA.

Abstract

For pre-exposure prophylaxis (PrEP) and microbicides to effectively prevent HIV, optimal treatment adherence is required. Adherence to these strategies, however, has not been sufficiently studied. This investigation systematically reviews oral PrEP and microbicide trials across 4 domains of adherence: 1) definition and measures used; 2) risks for non-adherence; 3) promotion strategies; and 4) effects on outcomes. Nineteen ($n = 19$) trials, with 47157 participants, published between 1987 and 2012 were identified. Reported mean adherence to microbicides was 79% and to oral PrEP 87%. Common risks for microbicide nonadherence were decreased motivation over time, sex with primary (noncommercial/casual) partners, and insufficient supply. Oral PrEP non-adherence risks were older age and medication side effects. Psychoeducation and outreach to participants and communities were frequently utilized promotion strategies. Most trials failed to systematically identify barriers and monitor and promote adherence, although adherence moderated outcomes. Recommendations for attending to adherence in future trials are provided.

Keywords

Adherence; Pre-Exposure Prophylaxis; Microbicides; Review

INTRODUCTION

Significant strides in HIV prevention have been achieved through the use of active pharmaceutical agents with individuals at-risk but currently HIV-negative.¹ These agents include antiretroviral treatments administered orally (i.e., oral pre-exposure prophylaxis, PrEP)^{2,3} and antimicrobial gels, creams, and films applied topically (i.e., microbicides).^{4,5} The effectiveness of PrEP in reducing incidence of HIV is strongly supported, and the evidence on the use of microbicides is promising.⁶

Correspondence to: Felix M. Muchomba, Global Health Research Center of Central Asia, Columbia University, 1255 Amsterdam Avenue, New York, NY 10027 (tel: (212) 851-2431, fax: (212) 851-2126, fmm2116@columbia.edu)..

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While these interventions are typically referred to as *biomedical* prevention strategies, in reality they are better characterized as *bio-behavioral* because of the significant behavioral factors that appear to impact their implementation and moderate their efficacy.⁷ Perhaps most importantly, individual adherence to the prevention protocols appears paramount to optimal response, yet may be difficult to achieve in those who are currently HIV-negative.^{8,9} Despite advances in adherence research and strategies in antiretroviral therapy,¹⁰ adherence to these biobehavioral prevention strategies (B-BPS) remains underdeveloped and under-researched. Adherence barriers encountered in antiretroviral therapy, such as depression,¹¹⁻¹³ substance use,¹¹⁻¹³ inadequate patient-provider relationships,^{12,14} lack of social support,^{12,15} negative publicity,¹² stigma,^{16,17} migration,¹⁶ poverty,¹⁸ inconvenient dosing frequency,¹⁴ distance to health facility,¹⁷ lack of coordination across health services,¹⁷ and limited involvement of community in program planning,¹⁷ may impede adherence to B-BPS. Investigation of adherence barriers and strategies to promote adherence is therefore required, for which effective adherence measurement is essential.¹⁹

This systematic review examines: 1) definitions and measures used for adherence in oral PrEP and microbicide research; 2) the individual-, partner-, agency-, community-, or structural- level risks for non-adherence; 3) strategies/interventions employed to promote adherence; and 4) effects of adherence on the major outcomes. Based on the review, recommendations for future research and implementation of B-BPS are offered.

METHODS

Empirical studies on oral PrEP and topical microbicides taken prophylactically by HIV-negative individuals to prevent HIV infection were searched using Medline, PsycINFO, and Cochrane Library databases. Searches were limited to clinical randomized controlled trials (RCTs) published in English between January 1, 1987 and January 1, 2012 that matched the MeSH keywords: HIV infections, anti-infective agents, vaginal creams, foams, and jellies, or gels, and any of the following terms: negative, seronegative, uninfected, pre-exposure, microbicide, prophylaxis, cellulose sulfate, tenofovir, carrageenan, naphthalenesulfonates, truvada, buffergel, PRO2000, or adenine. The comprehensiveness of search results was further verified by reviewing cited references, conference abstracts databases (Conference on Retroviruses and Opportunistic Infections Abstracts, International Aids Conference Abstracts, and International Aids Society Conference on HIV Pathogenesis and Treatment and Prevention Abstracts), and HIV prevention trials websites (HIV Prevention Trials Network, Microbicide Trials Network, Global Advocacy for HIV Prevention, and the Centers for Disease Control and Prevention). Studies were excluded when: 1) efficacy or effectiveness in preventing HIV infection was not assessed; 2) neither preliminary nor final outcomes were reported; 3) the treatment was a vaccine; or 4) the intervention being assessed was treatment of STIs other than HIV. The search identified 591 articles. A review of the abstracts by the research team resulted in the inclusion of 33 articles representing 19 RCTs.

For each eligible study, authors used a comprehensive template to extract features of the study population; preventive treatment; treatment protocol; study findings; as well as descriptions of adherence measurement; effect of adherence on outcomes; risks for non-

adherence; and strategies used to improve adherence. Other articles about the same study were identified and reviewed for additional details or verification of extracted data. The lead researcher in one was contacted for and provided additional details (J. Baeten, MD, PhD, written communication, February 2012).

Two authors (FMM and REG) separately identified risks and strategies and coded them as individual-, partner-, agency-, or community-level based on whether they were focused on the study participants, the sexual partners of study participants, study staff and structure, or leaders and members of the communities to which the participants belonged respectively. Non-adherence risks that involved both the study participants and their partners (i.e., lack of time to apply microbicide and sex acts with primary partner) were coded as both individual- and partner-level risks. Individual-, partner-, and community-level strategies were further grouped into psychoeducation,²⁰ outreach (i.e., contacting participants who missed follow up visits or to remind them to take treatment), and dosing (i.e., use of schedules and dose organizing tools). Agency-level strategies were further categorized into staff training, client-provider relations, and convenient locations and hours of operation. Inter-rater agreement surpassed 90%, with all differences resolved through discussion.

RESULTS

Study Characteristics

As seen in Table 1, the number of studies increased over time, with 2 studies conducted prior to 2000,^{21,22} 3 studies between 2000 and 2005,²³⁻²⁵ and 14 studies after 2005.²⁶⁻³⁹ Most ($n = 14$) studies were microbicide studies, and only 1 study had both microbicide and oral PrEP treatment arms.²¹⁻³⁴

Sample Characteristics

A total of 47157 participants were investigated across the 19 studies (see Table 1). The range in sample size was larger in microbicide studies (138 - 9385) than in PrEP studies (936 -5029), and mean sample size in microbicide studies was smaller (2557 vs. 2732).

All participants in microbicide studies were females at risk for HIV due to sexual activity,²¹⁻³⁴ with 6 specifying sex workers.^{21-23,25,32,34} Six (43%) microbicide studies excluded injection drug users,^{25,27,29,32-34} 1 study reported levels of drug (khat) use,²³ and the remainder did not report drug use characteristics of the participants.

Participants in oral PrEP studies also varied. Two studies included only female participants, of which 1 recruited sex workers.^{36,38} Of the 2 PrEP studies that had both female and male participants, 1 recruited HIV-serodiscordant couples.^{35,39} The remaining oral PrEP study recruited men and transgender women who had sex with men, with some participants reporting engaging in sex work.³⁷ Alcohol use was reported in 1 oral PrEP study.³⁷ No other studies reported drug or alcohol use among participants.

Study Retention

Five studies (26%) reported a retention rate, at 12 months, of 70% or less.^{23,25,28,29,38} On average, studies that reported recruiting sex workers had lower retention rates (73%) than

those that did not (87%). The most often-reported reason for participants' discontinuation was pregnancy.^{22,25,28-30,32-35,38} Studies did not report whether participants who dropped out were less adherent than retained participants prior to leaving the study.

Treatment Characteristics and Outcomes

One microbicide study employed a sponge,²¹ another employed a film,²² and the rest employed gels.²³⁻³⁴ Most ($n = 10$) microbicide studies required treatment application prior to every sex act. Oral PrEP studies largely used an Emtricitabine and Tenofovir Disoproxil Fumarate combination drug.^{31,35-37,39}

One microbicide treatment arm and 4 oral PrEP treatment arms were found to have a statistically significant protective effect.^{26,35,37,39} Eight microbicide and 3 oral PrEP treatment arms across 9 studies were terminated prematurely.^{23,28-32,34,36,38}

Adherence Measurement

Twelve studies reported 1 method of adherence measurement, 1 reported 2, and 6 reported more than 2. Eight studies (42%) measured adherence solely through self-report,^{22-25,27-29,32} 1 microbicide study used an applicator staining assay to test for vaginal insertion,³³ and 2 oral PrEP studies used blood level tests.^{36,37} Most (89%) studies assessed adherence once a month. Two studies assessed adherence quarterly.^{27,33} Four of the 12 microbicide studies that included self-report adherence measures used a 7-day recall period,^{24,28,29,32} 2 asked about microbicide use at the last sex act,^{30,33} 2 used a measure with a 7-day recall period and an additional measure regarding the last sex act or last working day for sex workers,^{25,27} 1 used a 1-month recall period,²⁶ and 3 did not report information on the self-report measures used.^{22,23,31} Both oral PrEP studies that included self-report measures used a 4-week recall period.^{36,37} Studies did not report psychometric properties of the self-report measures.

Self-report measures were biased upwards in the 2 studies that reported adherence rates from multiple measures.^{33,37} Adherence based on self-reports was much higher than adherence based on applicator staining assays (96% vs. 41%) in one of the studies and slightly higher than that based on pill counts (95% vs. 86%) and prescription refills (95% vs. 91%) in the second study.

Adherence to Microbicides

Three microbicide studies reported adherence rates in terms of proportion of participants correctly adhering to treatment protocols.^{27,30,33} Adherence rates reported in the remaining studies referred to average proportion of sexual acts in which microbicides were used. Adherence rates in microbicide studies ranged from 69% to 89% with a study mean of 79%. The average adherence rate for microbicides that required application prior to every sex act was higher (80%) than for microbicides that required only once or twice daily application (76%). The adherence rate was comparable between microbicide studies that reported including sex workers versus those that did not (81% vs. 78%); however, no study reported whether sex workers had a different adherence level from non-sex workers.

Adherence to Oral PrEP

Adherence rates reported in oral PrEP studies referred to average proportion of pills taken. Adherence rates in oral PrEP studies ranged from 69% to 97% with a study mean of 87%, indicating higher adherence rates to oral PrEP than to microbicides. The adherence rate was lower in oral PrEP studies that reported including sex workers versus those that did not (80% vs. 92%).

Impact of Adherence on Studies' Outcomes

One oral PrEP study and 3 microbicide studies analyzed and reported the impact of adherence on efficacy.^{26,30,33,37} High adherers, identified on the basis of pill counts, self-report, and dispensation records, achieved 41% higher efficacy compared to low adherers in the oral PrEP study. In a microbicide study that also reported a statistically significant treatment effect, high adherers, identified by comparing gel applicator returns and self-reported frequency of sexual intercourse, had a 26% higher efficacy. High adherers had a 20% higher efficacy, based on self report, and 16% lower efficacy, based on comparisons between gel applicator testing and self-reported frequency of sexual intercourse, in the remaining 2 microbicide studies, which did not report statistically significant treatment effects.

Risks for Microbicide Non-adherence

Few risks for non-adherence were reported in the studies included in this review (Figure 1). On average, 1 risk was reported in each study ($SD = 2.3$). Individual level risks to microbicide adherence identified were 1) heightened frequency of sex acts²⁶; 2) decreased motivation to use microbicides over time^{28,29,32}; 3) forgetting to use the microbicide³³; 4) increased number of sex acts with primary partners^{22,34}; 5) lack of time to apply microbicide or to replenish supplies³⁴; and 6) perceptions and beliefs such as fear of detection by partner, worry about potential side effects, concern that gel would accumulate from multiple applications within a short time, and a belief that gel use in sex acts occurring during menses is detrimental.³⁴ Partner-level risks for microbicide non-adherence were: 1) sex acts with primary partner^{22,34}; 2) lack of sexual partner cooperation³⁴; and 3) lack of time to apply microbicide while commercial sex client waited.³⁴ Insufficient supply was the only agency level risk for microbicide non-adherence.^{33,34} The most often cited risk for microbicide non-adherence was decrease in motivation to use the treatment over time followed by sex with primary partners and running out of treatment drug.

Risks for Oral PrEP Non-adherence

Most ($n = 4$) oral PrEP studies did not report non-adherence risks. Older age and medication side effects were the only risks for oral PrEP non-adherence noted.^{37,40}

Adherence Intervention Strategies Used

On average, 3.3 adherence intervention strategies were identified in each study. Individual-level strategies were the most common and included general psychoeducation, skills building, a personalized plan for adherence, adapting dosing protocols to participants' schedules, using calendars and pill organizers, outreach to participants who missed a visit,

and proactive outreach using cell phone alarms to remind participants to follow treatment protocols. Partner-level strategies involved either initial or ongoing psychoeducation intervention with the partner such as delivering study information to participants and their male partners as a couple. Agency level strategies included having convenient locations and hours of operation, positive client-provider relationships, and training staff and counselors. Community-level strategies included using community forums and boards to provide information about the study and to elicit feedback. Individual-level strategies were employed by all studies. Two studies employed partner-level strategies,^{27,30} 6 studies employed agency-level strategies,^{24,26,27,29,34,36} and 6 studies employed community-level strategies.^{22,26,27,30,36,37} Most intervention strategies were delivered by agency staff. In the study with discordant couples,³⁵ anecdotal evidence suggests that support from the HIV-infected partner, particularly the taking of medication together, reinforced adherence to oral PrEP (J. Baeten, MD, PhD, written communication, February 2012).

DISCUSSION

This systematic review of the state of science of adherence research in PrEP and microbicide studies found that few studies included detailed information on adherence. In those that did, adherence was associated with higher efficacy. Clearly, a lack of vigilance to adherence issues in trials may undermine estimates of the efficacy of these important B-BPS. This review follows and builds upon ongoing, but yet to be published, efforts of B-BPS researchers to promote adherence.

Assessing adherence is essential not only to determining accurate estimates of prevention efficacy but also for whom and in what circumstances adherence is problematic. As there is no “gold standard” for measuring adherence, multiple methods will likely be required.¹⁹ Studies that assessed adherence using multiple measures found self-report measures overestimated adherence. This is consistent with the adherence literature, which indicates that self-report is subject to overreporting bias particularly if individuals perceived negative consequences to admitting non-adherence.⁴¹ However, the majority of the studies reviewed in this paper used only one measure to assess adherence, many relying solely on self-report.

The most identified risks for non-adherence in microbicide research were a decline in motivation to use the product over time, sex with primary as opposed to casual or commercial partners, and insufficient supply. Risks for oral PrEP non-adherence cited were older age and medication side effects. Intervention strategies used to promote adherence to microbicides and oral PrEP were individual-, partner-, and community-level psychoeducation, adaptation of dosing protocols into participants' schedules, use of organizing tools, outreach to participants and communities, convenient locations and hours of operation, positive client-provider relationships, and staff training.

Adherence in microbicide studies was, on average, lower than in oral PrEP studies. Microbicide studies noted that sex acts with primary rather than casual or commercial partners, fear of detection of microbicide by partners, and lack of cooperation from partners hindered adherence, indicating that primary partner involvement might be important to promote adherence even when the strategies are women initiated and women controlled.

Vulnerable populations like sex workers and drug users may face unique lifestyle and social circumstances that undermine adherence to the treatment, but studies generally failed to report this information or simply excluded vulnerable groups.^{25,27,29,32-34}

Study limitations include the inability to geographically generalize findings, as most of the studies were conducted in sub-Saharan Africa. Comprehensiveness of the review may have been compromised by page limits in journals and lack of access to study protocols and manuals. Also, the likelihood of publication bias cannot be ruled out, despite the many non-significant findings published.

RECOMMENDATIONS FOR FUTURE TRIALS ON BIO-BEHAVIORAL PREVENTION STRATEGIES (B-BPS BPS)

Drawn from this review, five areas of recommendations for future research on B-BPS are outlined: 1) barriers to adherence; 2) strategies to promote adherence; 3) assessment of adherence and fidelity; 4) retention; and 5) impact of adherence on study outcomes (reduced incidence of HIV).

1. Pre-trial formative work should include a multilevel assessment of potential barriers to optimal adherence, especially in any vulnerable populations to be targeted. Stigma towards the use of B-BPS, mental health conditions such as depression and substance use, as well as structural barriers encountered in antiretroviral therapy adherence should be considered.¹¹⁻¹⁸ Development of a risk screen based on known risk factors for non-adherence is also recommended.
2. Trial protocols should incorporate evidence-based and culturally appropriate strategies to systematically promote adherence in all participants.⁴² Multilevel strategies that engage sexual partners, client-provider relationships, peer networks, communities, and case management can provide social support and address gender, community, and cultural norms regarding use of oral PrEP and microbicides.^{10,43} Couple-based approaches need to be provided as a choice for women in microbicide studies. Giving women an option to involve their partners may increase partner cooperation and improve adherence.^{44,45} While microbicides appear to be women initiated and women controlled; women also need education on possible partner responses and how to handle the responses and choice to involve the partner.
3. Trials procedures must include a priori plans to accurately and longitudinally monitor adherence. Measurements that are not subject to reporting bias, such as biomarkers⁴⁶ and applicator staining assays,^{47,48} are recommended as one of several measures used for triangulation. As use of self-report measures is likely to continue, attention to the psychometric properties of these measures, including their recall time frame, is needed to improve their validity and reliability. Additionally, research into factors that reduce bias of self-reports such as normalizing non-adherence is recommended. Adherence measurement should be supplemented by assessment of fidelity, defined as the extent to which core components of interventions are delivered as intended by the protocols.⁴⁹ Failure to implement a study with a high degree of fidelity could undermine a valuable prevention strategy.

4. Development of B-BPS that will not interfere with pregnancy is recommended. Restricting studies to women already on effective contraceptives is a strategy that one study has opted for to address high study discontinuation rates.⁵⁰
5. Analyses of efficacy should include (a priori) plans to investigate the role of adherence as a key effect moderator.

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FIGURE 1.
Frequency of Risks for Non-adherence and Adherence Intervention Strategies in Oral Pre-Exposure Prophylaxis (PrEP) and Microbicide Randomized Controlled Trials

TABLE 1
Characteristics of Oral Pre-Exposure Prophylaxis and Microbicide Randomized Controlled Trials and Participants

Authors	Sample Sex	Sample Age	Sample Characteristics	Sample Size	Study Retention Rate	Preventive Treatment ^c	Treatment Protocol	Study Findings ^d	Adherence Measurement ^e	Adherence to Treatment	Risks for Non-adherence	Adherence Intervention Strategies
Microbicides												
Abdool Karim et al. (2010) ^{26,51}	F	18–40	SA	NR	95%	Gel: TDF	Two doses: 12 hours pre and post sex act	Sig	1. Self-report 2. Applicator count	72%	1	8
Abdool Karim et al. (2011) ^{27,52}	F	18+	SA	Exc	94%	Gel: BufferGel Gel: PRO2000	One dose: 1 hour before sex act	Trend Non-sig	1. Self-report	81%		6
Feldblum et al. (2008) ²⁸	F	18–35	SA	NR	60%	Gel: SAVVY	One dose: before sex act	Non-sig	1. Self-report	78%	1	3
Halpern et al. (2008) ²⁹	F	18–35	SA	Exc	70%	Gel: Cellulose Sulfate	One dose: just before sex act	Trend	1. Self-report	81%	1	4
McCormack et al. (2010) ^{30,53}	F	16+	SA	NR	81%	Gel: PRO2000 2% Gel: PRO2000 0.5%	One dose: 1 hour before sex act One dose: 1 hour before sex act	Non-sig Non-sig	1. Self-report 2. Coital diaries 3. Applicator count 4. In-depth interview	89%		4
MTN (2011) ³¹	F	18–45	SA	NR	NR	Gel: TDF Oral: TDF Oral: FTC & TDF	One dose: daily One dose: daily One dose: daily	Non-sig Non-sig NR	1. Applicator count 2. Pill count 3. Self-report 4. In-depth interview 5. Focus group	- - - -		1
Peterson et al. (2007) ³²	F	18–35	SA SW	Exc	86%	Gel: SAVVY	One dose: 1 hour before sex act	Trend	1. Self-report	75%	1	4
Richardson et al. (2001) ²³	F	18–48	SW	Inc	65%	Gel: Nonoxynol-9	One dose: before day's first sex act	Non-sig	1. Self-report	75%		1
Roddy et al. (2002) ²⁴	F	18+	SA	NR	94%	Gel: Nonoxynol-9	One dose: 1 hour before sex act	Non-sig	1. Self-report	76%		2
Skoler-Karpoff et al. (2008) ³³	F	16+	SA	Exc	97%	Gel: Carraguard	One dose: 1 hour before sex act	Non-sig	1. Self-report 2. Applicator count 3. Staining assay	96% - 41%	2	2
Van Damme et al. (2002) ²⁵	F	16+	SW	Exc	68%	Gel: Nonoxynol-9	One dose: before sex act	Non-sig	1. Self-report	79%		1
Van Damme et al. (2008) ^{34,54}	F	18+	SW SA	Exc	88%	Gel: Cellulose Sulfate	One dose: 1 hour before sex act	Non-sig	1. In-depth interview	87%	10	2
Kreiss et al. (1992) ²¹	F	NR	SW	NR	84%	Sponge: Nonoxynol-9	One dose: before day's first sex act	Non-sig	1. Coital diary	81%		3
Roddy et al. (1998) ²²	F	18–45	SW SA	NR	73%	Film: Nonoxynol-9	One dose: before sex act	Non-sig	1. Self-report	87%	1	4
Oral Pre-exposure Prophylaxis ^f												
Baeten et al. (2011) ^{35,40}	F & M	NR	DC	NR	95%	Oral: TDF, Oral: FTC & TDF	One dose: daily One dose: daily	Sig Sig	1. Pill count 2. Random pill count 3. MEMS	97% - -	1	3

Authors	Sample Characteristics			Sample Size	Study Retention Rate	Preventive Treatment ^c	Treatment Protocol	Study Findings ^d	Adherence Measurement ^e	Adherence to Treatment	Risks for Non-adherence	Adherence Intervention Strategies
FHH (2011) ³⁶	Sex	Age	High Risk ^a	Drug Use ^b	1951	90%	Oral: FTC & TDF	One dose: daily	Non-sig	1.Self-report 2.Pill count 3.Blood level test 4.In-depth interview	95%	8
	F	18-35		NR						-		
Grant et al. (2010) ³⁷	M	18+	MSM SA SW	Inc	2499	82%	Oral: FTC & TDF	One dose: daily	Sig	1.Prescription refills 2.Self-report 3.Pill count 4.Blood level test	91% 95% 86% -	4
										-	1	
Peterson et al. (2007) ³⁸	F	18-35	SA SW	NR	936	37%	Oral: TDF	One dose: daily	Non-sig	1. Pill count	69%	2
Thigpen et al. (2011) ³⁹	F & M	18-39		NR	1219	90%	Oral: FTC & TDF	One dose: daily	Sig	1. Pill count	84%	1
Total Microbicide Mean (SD)	F=14 M=0	16-48	SA=11 SW=6	NR=7 Exc=6 Inc=1	2557 (2613)	81% (13%)	Gel=12 Film=1 Sponge=1	One dose: daily=3 Two doses: daily=1 Multiple doses: dose pre sex act=10	Sig=1 Trend=3 Non-sig=12	1.7 (1.3) Range=1-4	79% (6%)	Studies=14 Per study = 3.2 (2.0)
											(2.6)	
Total Oral PreP Mean (SD)	F=5 M=3	18-45	SA=3 SW=2 DC=1 MSM=1	NR=5 Exc=0 Inc=1	2732 (1764)	79% (24%)	Oral=6	One dose: daily=6	Sig=4 Trend=0 Non-sig=3 NR=1	2.6 (1.5) Range=1-4	87% (11%)	Studies=6 Per study = 3.2 (2.6)
											(0.5)	
Total Mean (SD)	F=18 M=3	16-48	SA=13 SW=8 DC=1 MSM=1	NR=11 Exc=6 Inc=2	2482 (2336)	81% (16%)	Gel=12 Oral=6 Film=1 Sponge=1	One dose: daily=8 Two doses: daily=1 Multiple doses: dose pre sex act=10	Sig=5 Trend=3 Non-sig=14 NR=1	1.9 (1.4) Range=1-5	81% (8%)	Studies=19 Per study = 3.3 (2.1)
											(2.3)	

^aHigh risk populations: DC = HIV serodiscordant couples; MSM = men and transgender women who have sex with men; SA = sexually active; SW = sex workers

^bDrug use in sample: Inc = included alcohol or khat use; Exc = excluded injection drug users; NR = drug use not reported

^cTDF = Tenofovir Disoproxil Fumarate; FTC & TDF = Emtricitabine & Tenofovir Disoproxil Fumarate combination

^dsig = protective, statistically significant (p < 0.05); trend = protective, marginally statistically significant (0.05 < p value < 0.1); non-sig = not protective or not statistically significant (p > 0.1)

^eMEMS = Medication Event Monitoring System (Aprex, Union City, CA, USA)

^fMTN (2011)³¹ study listed under microbicides is also included in oral pre-exposure prophylaxis as it contains both treatment arms