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Barriers and Facilitators of Adherence in User-Dependent HIV Prevention Trials, a Systematic Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors JA and KA jointly designed the study, managed the literature searches and performed data extraction. Author JA wrote the first draft of the manuscript. All authors reviewed several versions of the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Background: Suboptimal adherence to investigational products has been associated with ineffectual outcomes in clinical trials. This review provides a summary of factors that influenced adherence in HIV prevention trials.
Method: Our search included user-dependent trials that focused on sexual transmission of HIV. MEDLINE, Cochrane CENTRAL, Web of Knowledge v5.6, and Clinicaltrials.gov databases were searched as of August, 2012 and HIV/AIDS conference abstracts, March 2013.
Results: Twenty four HIV prevention trials were included. Main barriers related to adherence included; pregnancies, mobility and relocation from study area, adherence declining overtime as a result of fatigue, stigma and negative rumors about the clinical trials, and gel volume to be inserted perceived as too much. Other reported barriers were side effects, alcohol use, running out of study product after missing clinic visits, pill/gel sharing, forgetting to take/use study product, unplanned sex (in studies with coital-dependent dosing), concealing trial participation from partner, difficulty in sustaining high adherence levels in study products with a short half-life of 1-3 hours, and simultaneous use of multiple products. Key facilitators of adherence included; male involvement in trial

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related activities or disclosure of study participation to male partner, product acceptability, older age (>25 years), and high risk perception of HIV. Other facilitators were; routinizing pill taking, perceived enhancement of male partner's sexual pleasure, adequate supply of study product, good staff-participant relationship, less education, unannounced adherence support visits, and no overt side effects experienced as reported by participants.

Conclusion: Information on investigational prevention products should be packaged and delivered in ways that appeal to realities of participants' lives while remaining scientifically factual. Trials should customize adherence messages to address difficulties with study product use and prioritize community engagement to respond to issues around stigma, rumors and potential partner concerns. Additionally, efforts towards increasing HIV risk perception are central to optimizing adherence.

Keywords: Suboptimal adherence; HIV clinical trials; Africa; phase II/III trials; biomedical HIV trials.

1. INTRODUCTION

At the close of 2011, it was estimated that around 34 million people were living with HIV globally, of whom 22.9 million were in sub-Saharan Africa [1]. In response to the Millennium Development Goal six that focuses on halting and reversing the spread of HIV by 2015, there have been increased efforts on biomedical HIV prevention research [2]. Prevention methods such as male condoms, male circumcision, antiretroviral therapy, and oral pre-exposure prophylaxis (PrEP) have been proved to be effective prevention options. Other strategies being explored in randomized controlled trials (RCTs) include vaccines, vaginal rings and microbicides [3].

In user-dependent trials, the main determinant of effectiveness is adherence. A user dependent-trial is one in which the investigator relies on the participants to use/take the study product under their own volition. Suboptimal adherence to investigational products was one of the main factors that was cited as having contributed to poor outcomes in previous user-dependent RCTs on vaginal diaphragm, vaginal microbicides, herpes simplex virus type 2 (HSV2) suppressive therapy and oral PrEP [4–17].

Adherence is more than simply remembering to take medications; rather, it is a complex issue involving social, cultural, economic, and personal factors [18]. We present a review of documented barriers to and facilitators of adherence in phase II/IIb and III HIV prevention clinical trials hosted wholly or partly in Africa. We focus on Africa as the region where these interventions are likely to be rolled-out and have the greatest potential impact in reducing the burden of HIV, especially among women.

2. METHODS

2.1 Search Strategy

A search was made in MEDLINE via PubMed, Cochrane CENTRAL, Web of Knowledge v5.6 and NLM Gateway databases for articles meeting the inclusion criteria as of August 2012. Search terms included: 'HIV', 'prevention', 'randomized controlled trial', 'controlled clinical trial', 'trial', 'pre-exposure prophylaxis', 'microbicide' and 'Africa'. Reference lists were

scanned for relevant articles and some study authors contacted to get more information. Conference abstracts were sought from AEGiS and other recent HIV related conferences such as International Microbicides Conference, Conference on Retroviruses and Opportunistic Infections (CROI), and International AIDS Society Conference on HIV Pathogenesis and Treatment (IAS) as of March 2013. Clinicaltrials.gov and WHO International Clinical Trials Registry Platform were searched to identify on-going and recently completed trials. Only articles published in English were considered.

Inclusion criteria for trials in this review were; 1) unit of randomization was an individual and 2) completed phase II/IIb and III HIV biomedical prevention trials conducted wholly or partially in Africa that focused on sexual transmission of HIV.

Of note is that, in this review the definition of adherence has been restricted to the extent to which the behavior of a study participant in pill taking or gel or diaphragm usage corresponds with agreed recommendations from the respective study protocol as implemented by study staff.

2.2 Data Extraction

Data extracted from each study included; study design; location; population size; type of intervention; duration of follow-up; adherence measurements, levels and the impact of adherence levels on trial outcomes; barriers to adherence; and facilitators of adherence. Data was independently extracted by the two reviewers (JA and KA).

3. RESULTS

3.1 Articles Reviewed

A total of 13,126 citations were retrieved from the electronic databases, of which 24 met the inclusion criteria, underwent a full length review, and were all included [4–14,16,17,19–29]. Additionally, 96 abstracts were reviewed but excluded as the contents were unrelated to the topic of interest. The remaining 13,006 were excluded as their titles were not relevant (Fig. 1).

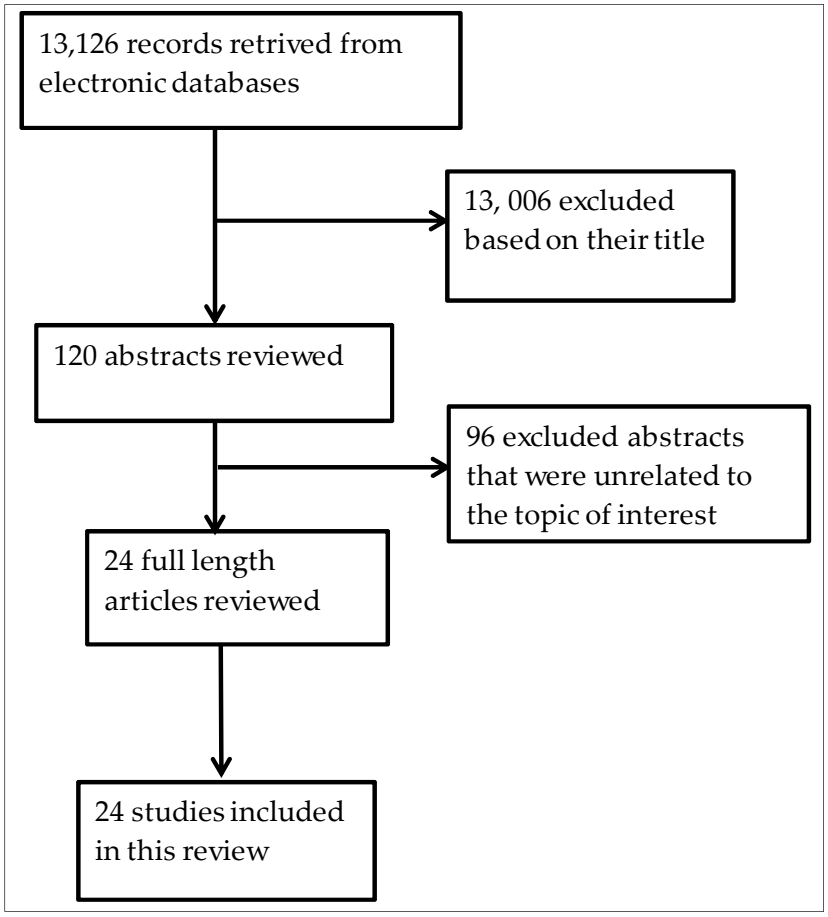

Fig. 1. Flow chart of trials included in these review

3.2 Characteristics of Selected HIV Prevention Trials

Approximately 51,000 individual participants were enrolled in 21 trials, of whom 11.4% were men [4–17,21,24–29], while the remaining three enrolled 9,926 couples [20,22,23]. The mean age reported in 12 trials was 25.5 years [4,6–8,10–12,14,17,24,26,30]. Sixteen of the 24 trials were phase III [5–8,11,12,16,19–23,25,27,29], one was phase II/III [28], two were phase IIb [10,17] and five were phase II/IIb [4,13,14,24,26]. Twenty trials enrolled HIV negative participants [4–13,15–17,21,24–29] and four enrolled both HIV negative and HIV positive participants [14,20,22,23]. Of these four, the study intervention targeted negative participants in one trial [20], positive participants in two trials [22,23] and both HIV negative and positive participants in one trial [14]. Of note, in the Cohen et al. trial [23] adherence was being monitored in persons who were receiving actual treatment of their own HIV infection. Hence, sources of motivation to adhere may have differed in this group compared to those in other studies where efficacy of the intervention was unknown and a large number of them were healthy individuals. Thus, adherence may not have been a priority among the latter group.

Most trial sites were located in South Africa (n=14) [4–6,8,10,12,17,19,21–25,28], six trial sites were in Zimbabwe [14,17,19,21,23,24], five trials sites each in Kenya [6,20,22,23,29] and Uganda [5,17,20,22,25], four trials sites each in Tanzania [6,13,22,25] and Zambia [21,22,24,25], three trial sites in Botswana [22,23,27], two trial sites each in Malawi [23,24], Nigeria [9,26], Benin [5,28], Cameroon [16,26] and Ghana [11,26], and one trial site each in Cote d'Ivoire [28] and Rwanda [21].

Thirteen trials evaluated microbicides of which 11 were vaginal gels [4,5,7,9–12,17,24,25,28], one a vaginal film [16] and one a vaginal sponge [29].Three trials evaluated HSV2 suppressive therapy [13,21,22], two evaluated diaphragm usage - one was with a microbicide and lubricating gel [14] and the other with a lubricating gel [19], six trials evaluated oral PrEP among different study populations [6,8,17,20,26,27], and one trial evaluated treatment as prevention of HIV [23]. Duration of follow up ranged from 1 month - 78 months (Table 1). Six trials were prematurely closed [5–7,9,11,26]. In the VOICE trial, oral tenofovir disoproxil fumarate (TDF) and vaginal gel TDF arms were prematurely closed [17]. The above-mentioned trials reported no major safety concerns except three [5,9,28].

3.3 Methods for Measuring Adherence

Adherence was assessed by using both direct and indirect methods (Table 1). Indirect methods included; self-reports in face to face interviews about the number of missed doses over a specified time period using case report forms (CRFs) or questionnaire or audio computer-assisted self-interviews (ACASI) in 18 trials [4–12,16,17,19,21,24,25,27–29,32] and counting returned pills/applicators (12 trials) [4,6,8,10,17,20–23,26,27,30]. Direct methods included testing vaginal secretions on the gel applicators (one trial) [12], monitoring drug products in urine (one trial) [30], and blood (six trials) [6,8,20,27,33].

3.4 Interventions to Improve Adherence

In three trials, interventions to improve adherence were implemented prior to trial initiation by conducting site preparedness activities and incorporating ideas from potential participants and other stakeholders into adherence support programs [6,34,35]. One out of the two trials [6] employed a vitamin run-in period where the participant would take a vitamin similar in size to the study pill once a day for up to 4 weeks. Additionally, direct observation of participant swallowing a vitamin was done prior to randomization; if the participant was unable to swallow the vitamin they could not be enrolled in this trial [6]. Other adherence support programs included: adherence counseling done in 23 trials, unannounced adherence support visits/pill counts in two trials [20,30], the use of job aids such as flip charts and informational leaflets, and providing adherence aids such as pill boxes and calendars in six trials [6,20,21,30,36,37].

Table 1. Adherence Levels

First author, reference	Number of participants	Duration of participation	Adherence levels				
			Self-reports	Pill/ applicator count	Biomarker of product use	Plasma drug level monitoring	Intracellular drug concentration
Pre-exposure prophylaxis							
Microbicide Trial Network [17]	3,019	12-36 months	90%	90%	-	TDF/FTC-29% TDF-28% Gel-23%	-
Baeten et al.[20]	4758 couples	36 months	-	97%	-	82%	-
Van Damme et al.[6]	2,120	12 months	95%	85%	-	<40%	-
Grant et al.[8]	2,499	median, 1.2 years; maximum, 2.8 years	93%	93%	-	50%	44%. [31]
Thigpen et al.[27]	1219	12 months	94.3%	84%	-	81%	-
Peterson et al.[26]	936	12 months	-	69%	-	-	-
Microbicides							
Microbicide Trial Network [17]	2010	12 months	90%	90%	-	23%	-
Abdool Karim et al.[10]	889	30 months	82.4%	72.2%	-	-	-
Van Damme et al.[5]	1,644	12 months	87%	-	-	-	-
Halpern et al.[9]	1,398	12 months	81%	-	-	-	-
The Carraguard Phase II South Africa Team.[4]	400	6-12 months	80%	84.5-96.6%	-	-	-
Skoler-Karpoff et al.[12]	6,202	9-24 months	96%	-	Applicator testing 42.1%	-	-
Abdool Karim et al.[24]	3101	12-30 months	81.10%	-	-	-	-
Peterson et al.[11]	2,142	12 months	76%	-	-	-	-
Feldblum et al.[7]	2,153	12 months	78%	-	-	-	-
McCormack et al.[25]	9385	12-24 months	89%	-	-	-	-
Roddy et al.[16]	1,292	at least one year; mean 14 months	87%	-	-	-	-
Kreiss et al.[29]	138	1-46 months	81%	-	-	-	-
Van Damme et al.[28]	892	Open cohort design with continuous enrolment	76%	-	-	-	-
Herpes simplex virus - Type 2 suppressive therapy							

Celum et al.[21]	3172	18 months	94%	86%	-	-	-
Celum et al.[22]	3408 couples	24 months	-	96%	-	-	-
Watson-Jones et al.[30]	1,305	30 months	-	90%	55% in urine in acyclovir group & 5% placebo group	-	-
Diaphragm							
Van der Straten et al.[14,32]	119	6 months	58%	-	-	-	-
Padian et al.;[15] Van der Straten et al.[19]	4,948	12 - 24 months	49%	-	-	-	-
Treatment as prevention							
Cohen et al.[23]	1763 couples	60 - 78 months	-	77%	-	-	-

3.5 Evaluation of Adherence Support Program

Evaluation of effectiveness of adherence support programs has not been conducted as part of clinical trials. Of the 21 studies that enrolled individuals, 14 reported that suboptimal adherence was a key factor that contributed to poor trial outcomes [4–17]. On the other hand, two trials that enrolled serodiscordant couples [20,23] reported effective trial outcomes which was attributed to high adherence levels [20,22,23]. Conversely, HSV2 suppressive therapy to reduce HIV-1 transmission among serodiscordant couples had poor outcomes despite reported high adherence levels; the authors suspected strain variation resulting in inherent acyclovir resistance among HSV strains from Africa, or unappreciated differences in acyclovir absorption or pharmacokinetics [38], or inability of acyclovir to diminish inflammatory response [39].

3.6 Dose Response Relationship

To underscore the importance of adherence in determining trial outcomes, two trials indicate a dose response relationship between level of effectiveness and level of adherence, based on pill/applicator counts, self-reports and pharmacy records. For instance, in the CAPRISA 004 study, adherence of >80% was associated with 54% protective efficacy, 50-80% adherence was associated with 38% efficacy, and <50% was associated with 28% efficacy [10]. In iPrEx trial, protective efficacy was 73% in those with ≥90% adherence, 50% among those with 50-90% adherence and 32% among those with <50% adherence [8].

3.7 Barriers to Adherence

3.7.1 Participant related

Thirteen of the 23 barriers reported were participant related and included; pregnancies resulting in participant being taken off product (15 trials) [5–7,9–11,14,20–22,24,25,27,40,41] high rates of relocations and frequent trips away from study area (eight trials) [5,6,9,21,27,28,34,42,43], adherence declining over time due to fatigue [six trials] [7,8,10,11,25,44], alcohol use (three trials) [30,36,45], insufficient supply of study product due to missed visits (three trials) [34,43,46], pill/gel sharing (three trials) [34,42,45,47], forgetting to take/use the study product [three trials] [12,43,46], unplanned sex (two trials) [34,48], participants less than 25 years (two trials) [11,17], low risk perception of HIV (one trial) [49], stress (one trial) [36], changes to routine (one trial) [36] and concurrent illnesses (one trial) [36].

3.7.2 Product characteristics/ study design

Common barriers related to product characteristics included; side effects as a result of study product usage (14 trials) [4,6,8,10,12,14,16,20,23,25,27–29,43]; volume of gel to be inserted per sexual act perceived as too much, resulting in gel usage being regarded as messy (four trials) [34,50–52]; study pill having a short half-life (two trials) [42,53]; decreased sexual pleasure as a result of using the study product (one trial) [32]; and large size of study pill (one trial) [43]. Simultaneous use of 2-4 study products (two trials) [15,32] was a barrier related to study design.

3.7.3 Interpersonal relationships

Three barriers reported on interpersonal relationships included: stigma related to trial participation and negative rumors about the trial (four trials) [34,36,54,55], concealing study product from primary partner for fear of negative reaction (two trials) [34,52], single women (one trial) [17], and poor staff-participant relationship (one trial) [51].

3.8 Facilitators of Adherence

3.8.1 Participant related

Eleven out of 17 factors that enhanced adherence included; product acceptability (nine trials) [4,10,19,32,34,43,46,56,57], study participants being above 25 years of age (seven trials) [17,19,28,30,32,58,59], high risk perception of HIV infection (six trials) [19,32,34,48,58,60], establishing a routine of pill taking [four trials] [36,43,45,60], adequate supply of study product (three trials) [30,43,58], none or minimal education (two trials) [28,59] unannounced adherence support visit ahead of appointment date (two trials) [30,61], not relocating or having less trips away from the study area (one trial) [30], not pregnant during trial participation (one trial) [30], understanding of the three key trial concepts (randomization, blinding and placebo) at first attempt of pre-consent comprehension assessment (one trial) [30], and using oral contraceptives at screening (one trial) [30].

3.8.2 Product characteristics/ study design

Two factors based on product characteristics that enhanced adherence were; gels' lubricating properties resulting in a great effect on sexual pleasure (four trials) [34,48,51,57], and reporting no overt side effects when using the study product (two trials) [9,34]. As part of study design, adherence was also enhanced by couple-based counseling (one trial) [60].

3.8.3 Interpersonal relationship

Three factors that contributed in facilitating adherence included: male involvement in trial related activities and disclosure of study participation (10 trials) [10,19,32,34,45,48,51,57,60,62], good staff-participant relationship (three trials) [34,45,60], and being married (one trial) [17].

4. DISCUSSION

There were several barriers to adherence noted in this review. Four trials [5,7,9,11] with interventions that had both anti-HIV and contraceptive activities had a similar and high number of pregnancies in both arms, which is indicative of poor adherence to the study product. The common factor in these trials was that they recruited younger women who are considered to be at a higher risk of acquiring HIV [1] and also among whom pregnancy intentions are highest [63,64]. Current HIV prevention trials that only have anti-HIV activities exclude women with intentions of becoming pregnant during study participation, provide contraceptive counseling and most study-approved contraceptive methods on-site. As such, future trials in multipurpose technologies designed to prevent unintended pregnancy and HIV should take into account user needs and extraneous factors such as changes in sexual partners, perceptions of HIV risk vis-a-vis pregnancy intentions, and similar activities that may have direct impact on adherence.

Additionally, FEM-PrEP trial [65] reported that most participants on oral contraceptive who became pregnant also had lower adherence to study pills by pill count, suggesting, on the one hand, that adhering to both oral contraceptives and study pill may have been burdensome, and on the other hand, that a more-than-anticipated rate of pregnancy in the course of a trial could be indicative of more widespread state of poor adherence to the study product as well. Trial investigators should always monitor pregnancy rate among participants and use it as a red flag that adherence approaches in use may not be working.

Fourteen trials reported that participants experienced side effects, and though not directly mentioned as a barrier, there is reason to believe that the worry about potential side effects [34] and the fact that not taking the study product resulted in a relief of side effects [36], might have led to suboptimal adherence. One way to mitigate this would be to clearly and systematically educate participants on what side effects to expect and how to address them through home management. A study evaluating ARV program rollout in Uganda, Tanzania and Botswana [67] reported that adherence in Botswana was higher because patients received counseling on expected side effects unlike the other two sites where there was no or minimal pre-treatment counseling.

Optimal adherence declined over time mostly in trials that had follow up period of more than 12 months [7,8,10,11,25,44], probably as a result of fatigue. To adjust for this, modification in the trial design may include having a large sample size with a shorter follow-up period, or following up all subjects for HIV infection for a specific time (for example, 6 months) after the last subject has been enrolled. Thus, if the trial takes 18 months to enroll all subjects, follow-up will range from 6 months for the last enrolled subject to 2 years for the first enrolled subject [66]. Period of follow up should thus become an important consideration in the design of trials, and the shortest period to obtain scientifically valid results is recommended.

Disclosure and male involvement activities implemented prior to and during the trial period enhanced compliance with study product use [19,57,68]. Trials that enrolled serodiscordant couples reported high adherence levels for predicable reasons. For instance, in Baeten et al. [20] some couples reported taking their pills at the same time (cotrimaxozale by HIV-infected partner and study pill by uninfected partner) [60]. Bringing partners and others who may influence participant's adherence or participation in the study in a pre-enrollment visit - where the study is explained to each couple or other family members - should be integrated into adherence support programs. This may reduce suspicion, encourage women to apply/take their product more openly and get the partners or other family members to remind them of product use. In addition, given that disclosure by younger women may be a bigger challenge, investigators may consider excluding potential participants who report that their partners may have problems with their participation in the study, because this may be indicative of those who may not use the product should it show efficacy and be made available.

However, there are also concerns over how disclosure can be exercised by disempowered women in relationships. A woman's own assessment of her relationships and risks, influenced by social and cultural norms for behavior, will likely drive her decision on whether to use a microbicide, and on whether to use it covertly [69]. Marketing products as a way to "enhance pleasure" or to maintain a "clean and healthy vagina" could make it easier for women to use microbicides [69]. We believe that one of the barriers to obtaining high adherence may lie in both content and approach - factual information delivered in a highly professional manner may not be appreciated by some participants; instead, a more interactive and informal delivery approach with inclusion of side issues such as potential

effect of product on sexual pleasure and genital hygiene may resonate better with them. We suggest brief pre-trial qualitative study to identify preferred delivery approaches and what messages trials should communicate to participants, which can be included alongside factual information.

In trials that reported suboptimal adherence, we hypothesize that participants may not have taken their study participation seriously due to low risk perception. For instance, high risk perception in Partners PrEP was a contributor to high adherence levels as compared to FEM-PrEP where there was low risk perception. Additionally, in the iPrEx study, adherence analysis showed that participants tampered their adherence according to their level of risk[58]. Thus, use of daily vaginal gels and PrEP did not fit into the social, behavioural and economic contexts of the populations targeted by the trials. Further, it has been reported that participants were aware that trial staff had no way of knowing whether they used the study product or not [70].

Nonadherence to product use in a randomized controlled trial can result in failed studies and type 1 error, where a potentially effective intervention is incorrectly rejected because participants did not adhere at sufficient levels to provide a valid test of the treatments studied [18]. Reduced power to detect an effect was apparent in two of the four PrEP phase III trials that reported suboptimal adherence. However, FDA approved the use of oral TDF/FTC as a prevention method for HIV-negative people based on the two trials that reported efficacy. Although we know that the pills work when taken, non-adherence in the FEM-PrEP and VOICE trials has introduced extra caution in considering the application of the results, and will most likely limit the target populations among whom countries may use PrEP.

Some of the approaches of increasing accountability from study participants in adherence measurement is to conduct unannounced adherence support visit and to employ real time pharmacokinetic monitoring. With care taken not to unblind the trial prematurely, drug levels in participant's blood (plasma and/or intracellular drug concentration) or hair can be measured during stipulated study visits and information obtained matched with self-report, pill counts and pharmacy refill. Motivational interviewing technique would then be employed when giving feedback to the participant. This means that challenges to adherence will be addressed and improved in "real time."

Another novel system now available for direct measure of study pill utilization comprises of an ingestible sensor (the Ingestion Event Marker™ [IEM™]). IEM, the size of a sand grain, is integrated into a pill and when ingested it sends a signal to a patch worn on the skin. The information is then relayed to a mobile phone with software to a clinician or researcher [71]. Additional strategies include the use a breath test to monitor adherence in both oral medications (such as HAART) [72] and vaginal gels [73]. Ester taggants are added to vaginal gels and the food additive while 2-butanol are added to oral medications. When ingested or inserted into the vagina, they are metabolized in the liver and the exhaled alcohol and ketone metabolites are measured by the breath test. The results of each breath test are recorded by the device. While we include these two approaches, they are still under development and their use and acceptability have not been documented.

Poor adherence was also related to simultaneous use of multiple products during trial participation. In the two diaphragm studies [15,32], participants in the active arm were required to use diaphragm, condom, contraceptive and the gel, and this was cited as reason for difficulty with compliance. This and other limitations underscore the need to develop sustained release formulations such as vaginal rings and injections that do not require daily

usage or applications before sexual intercourse. Currently, two studies designed to determine whether a monthly vaginal ring that delivers the ARV drug dapivirine helps prevent HIV infection in women are being conducted in Africa [74].

Apart from receiving quality health care we believe that compensation for time may have been a major reason for coming for clinic visits but not taking their study product. For example, the Medicines Control Council (MCC) of South Africa has predefined reimbursement rate of 150 Rand ($16.67) for each scheduled clinic visit throughout the duration of the trial. This figure may be reasonably high as compared to minimum hourly wage for domestic workers which range from 4.85 Rand ($0.53) to 7.06 Rand ($0.78) [75]. For women who have no other means of income, this may have been the motivating factor encouraging enrolment into a study [70,76]. Similarly, Tanzania's lowest minimum wage is $0.26 per hour [77]; however participants received as much as 3000 Tanzanian Shillings (approximately $3; per the currency conversion rate during that period) as reimbursement for their time [13]. Thus, there is need to provide compensation for time based on minimum wage guideline of a specific country in order to minimize the tendencies to enroll in trials for purposes of financial gain.

A major limitation of this systematic review is that where several methods of assessing adherence were used even in the same trial [6,8,12,20,27,30] different levels of adherence were obtained. For example, we observed that objective measures had lower readings than subjective measures [6,8,12,30], which is consistent with other studies in which ARV users tended to overestimate their pill taking behavior when interviewed [78,79] mostly likely due to social desirability reporting or recall bias. Thus, the determinants of non-adherence which we have reported may differ between those that used objective markers and those that did not. Additionally, we consider as a limitation the fact that this review focused on HIV prevention trials conducted wholly or partially in Africa, thus it may be difficult to generalize the findings to the rest of the world or to HIV treatment trials or to adherence among non-HIV trials. However, as the region where trial products will be mostly consumed, focusing on sub-Saharan Africa can be also viewed as strength. Furthermore, although the search strategy was extensive, there is a possibility that this review may not have captured all studies that reported on factors affecting adherence in HIV prevention trials.

Overall, we observe that most of the barriers identified in this review can be addressed by understanding the research communities and characteristics of potential participants – their reproductive and sexual health needs and desires that may impact on product adherence, their perceptions of personal risk for HIV infection vis-à-vis adherence to a medical product with strict dosing schedule and how the product should be packaged and delivered in ways that appeal to participants' day-to-day life situations, such as "gel improves sexual pleasure to both women and their partners."

5. CONCLUSION

Multiple trials have confirmed that PrEP, treatment as prevention and ARV based microbicides work to reduce the risk of acquiring HIV but only when used as instructed. Due to sub-optimal adherence, a number of studies failed to demonstrate significant effect of these products. This was particularly evident among young women, yet this is the group most at risk of HIV and among whom effective HIV prevention options would be most relevant. Two large PrEP studies – FEM-PrEP and VOICE – demonstrated without a shadow of doubt that investigators can no longer rely on self reported adherence or pill count, because these measures grossly overstate true adherence. Our paper has summarized

documented barriers to and facilitators of adherence in user-dependent products, and has suggested strategies that investigators can consider to improve and monitor adherence when designing future clinical trials. We have suggested, for example, that to inform trial design, investigators should obtain views of potential participants, their significant others, and their communities regarding how adherence messages should be customized to appeal to their lived experiences; how to raise participants' perception of risk so that they take adherence seriously; and how to build research literacy among participants so that they appreciate the critical role their participation in and compliance with trial procedures play in shaping the future of HIV prevention landscape at local, regional and global levels.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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