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Systematic Review

Tenofovir-based HIV Pre-Exposure Prophylaxis for Sub-Saharan African Women at High-risk of Acquisition: An Integrative Systematic Qualitative Evidence Synthesis of Factors Affecting Adherence

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Abstract

Introduction: Women from Sub-Saharan Africa remain at substantial risk of HIV acquisition and require urgent interventions to mitigate this issue. Oral pre-exposure prophylaxis offers a viable option. Unfortunately, it was ineffective during clinical trials in this population due to poor adherence. This systematic review has been conducted in order to understand the factors uniquely affecting adherence in this population.

Methods: Five databases (Embase, Medline, CENTRAL, Web of Science and ClinicalTrials.gov) were searched for relevant observational and qualitative studies reporting the factors affecting adherence. Titles and abstracts of returned articles were assessed for eligibility, leading to retrieval of full texts. Quality and risk of bias assessments were done before data extraction. Thematic qualitative evidence synthesis was done for factors affecting adherence.

Results: Sub studies and ancillary studies of the three main clinical trials were retrieved, employing quantitative and qualitative methods to assess factors affecting adherence to tenofovir-based pre-exposure prophylaxis. Identified themes were grouped into five categories based on a modification of Ickovics and Meisler's conceptual framework. These are individual, partner, social/community, product/drug and research related factors. Within each category, barriers and facilitators of adherence were placed. Significant barriers to uptake pre-exposure prophylaxis were identified.

Conclusion: The success of future clinical trials on HIV prevention methods among Sub-Saharan African women, and the successful rollout of preventive public health interventions will depend on adequately addressing barriers to adherence. Therefore, clinical and public health researchers must aim to understand these factors, to optimise uptake and benefit from the interventions.

Keywords: Human Immunodeficiency Virus, Pre-exposure Prophylaxis, Adherence, Sub-Saharan Africa, Women

Introduction

Four decades into the epidemic, women and girls from Sub-Saharan Africa (SSA) remain at a differentially high risk of Human Immunodeficiency Virus (HIV) acquisition. UNAIDS estimated that 59% of the incidence of HIV infections in 2019 occurred in this population.[1] Reducing new infections in this group remains a public health priority for epidemic control.[2] An array of biomedical interventions have been introduced, which must work in tandem to significantly reduce infections.[3] Among these, pre-Exposure Prophylaxis (PrEP) has remained a promising intervention.[4] Oral PrEP is based on Tenofovir Disoproxil Fumarate (TDF) combinations, and has been licensed since 2015 for use by at-risk groups including men-who-have-sex-with-men (MSM) and transgender women (TGW).[5] Dapivirine vaginal rings have also shown success[6] and are now included by the World Health Organisation (WHO) among PrEP regimens. Vaginal rings bring exciting prospects for Multi-purpose Prevention Technologies (MPTs), which include hormonal contraceptives and Sexually Transmitted Infection (STI) prophylaxis.

As the search for effective HIV vaccines remains elusive, the use of PrEP continues to provide a promising prospective for epidemic control.[7,8] Unfortunately, despite proving effective in populations such as MSM and TGW,[9] TDF-based PrEP was ineffective or even futile in placebo-controlled clinical trials conducted among SSA women due to very low levels of adherence to study products.[10] To achieve optimal usage of PrEP in the population that needs it the most, barriers to uptake

must be identified, understood and robustly addressed. We therefore undertook an integrative systematic review of adherence to TDF-based PrEP and the factors affecting the same uniquely among SSA at high risk of HIV acquisition. The factors which have been identified as affecting adherence are described in the present review.

Materials and Methods

Protocol and Registration

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance.[11] Additional guidance was obtained from the Cochrane Handbook of Systematic Reviews and Meta-analysis for Interventions.[12] The protocol was not registered in PROSPERO.

Eligibility Criteria

The studies were restricted to heterosexual SSA women at risk of HIV acquisition. Only observational and qualitative studies reporting factors affecting adherence to TDF-based PrEP among women in SSA were included. These studies were sub studies or ancillary studies of primary RCTs evaluating the effectiveness of tenofovir-1% (TFV-1%) vaginal gel, oral TDF and oral truvada (TDF-FTC) in preventing HIV acquisition against their respective placebos. Studies which evaluated adherence to other PrEP or not involving heterosexual women from SSA were excluded. No language restriction was placed.

Study Designs

Appropriate designs for the evaluation of factors affecting adherence including cross-sectional studies, case-control studies, cohort studies, purely qualitative studies and studies employing mixed methods (both quantitative and qualitative) were evaluated in the present study. Hence, this study was an integrative systematic review.

Information Sources and Search Strategy

A systematic literature search in OVID Medline, OVID Embase, Web of Science, CENTRAL and ClinicalTrials.gov was conducted from 1 January 2020 to 31 July 2020, to identify clinical trials testing the effectiveness of TDF-based PrEP among SSA women and their sub studies and ancillary studies evaluating adherence qualitatively or quantitatively. Multiple databases were searched to limit bias as recommended by the Cochrane Collaboration. To develop and refine inclusion criteria for the literature search, the PICOS strategy was applied. The population included the heterosexual SSA women at risk of HIV acquisition. The interventions have been described above, and the outcomes were effectiveness against HIV acquisition, adherence to study products and measures of adherence to study products. Results of effectiveness were reported in a previous publication.

The search strategies were constructed from combinations of Medical Subject Headings (MeSH) and keywords, which were adjusted for individual databases by the Principal Investigator (GM). The Cochrane highly sensitive strategy for identifying studies in Medline: sensitivity-maximising version (2008 revision); OVID format was used to filter studies in Medline whilst the Scottish Intercollegiate Network (SIGN) search filters were utilised in Embase. No filters were applied in the remaining databases. Subject terms were exploded in OVID databases to include subordinate terms in the search hierarchy, and where necessary free text terms were truncated to search for variant endings in order to capture variant endings. Boolean operators AND/OR were utilised to combine search terms. Where it was felt appropriate, citation search was done to identify additional literature, but no grey literature searches were done as it was expected that the eligible studies would be retrieved from peer-reviewed journals.

Results from each database were imported into Mendeley desktop version 1.19.4 and reduplicated. GM screened the titles and abstracts of the remaining studies for eligibility. All eligible studies were accessed. All studies for which eligibility could not be assessed based on the abstract were obtained in full for further assessment. Detailed search strategies for MEDLINE and EMBASE are included as Appendix 1 and Appendix 2, showing the appropriate MeSH terms, as recommended by PRISMA guidance.

Data Collection Process and Data Items

A pretested data extraction sheet was developed in Microsoft Excel 2013 to facilitate data collection. Study lead author, year of publication, geographical location, source of funding, journal of publication and number of participants were extracted. Factors affecting adherence were extracted from the articles. The particular outcome specific headings used in this review included adherence measures, adherence and

effectiveness as well as factors affecting adherence.

Risk of Bias Assessments

The Newcastle-Ottawa scale was used to determine the risk of bias for observational studies. The observational studies mainly employed mixed methods, with both quantitative and qualitative components. There being no specific risk of bias assessment tool for qualitative studies, a Critical Skills Appraisal Programme (CASP) checklist was used to assess the usefulness of the results. It looked at three broad issues, namely validity of the results, the actual results and whether the results will be helpful in the local setting, in which the study was conducted. Due to their nature, qualitative results are not easily generalizable outside their context owing to non-random sampling and lack of uniform interpretation.

Qualitative Evidence Synthesis

In order to identify barriers and facilitators to adherence, qualitative thematic evidence synthesis was done. A simple conceptual framework, developed from Ickovics' and Meisler's original framework[13] was used to categorise the factors into individual, partner, society/community, study product and research related factors. The conceptual framework is illustrated in Figure 1.

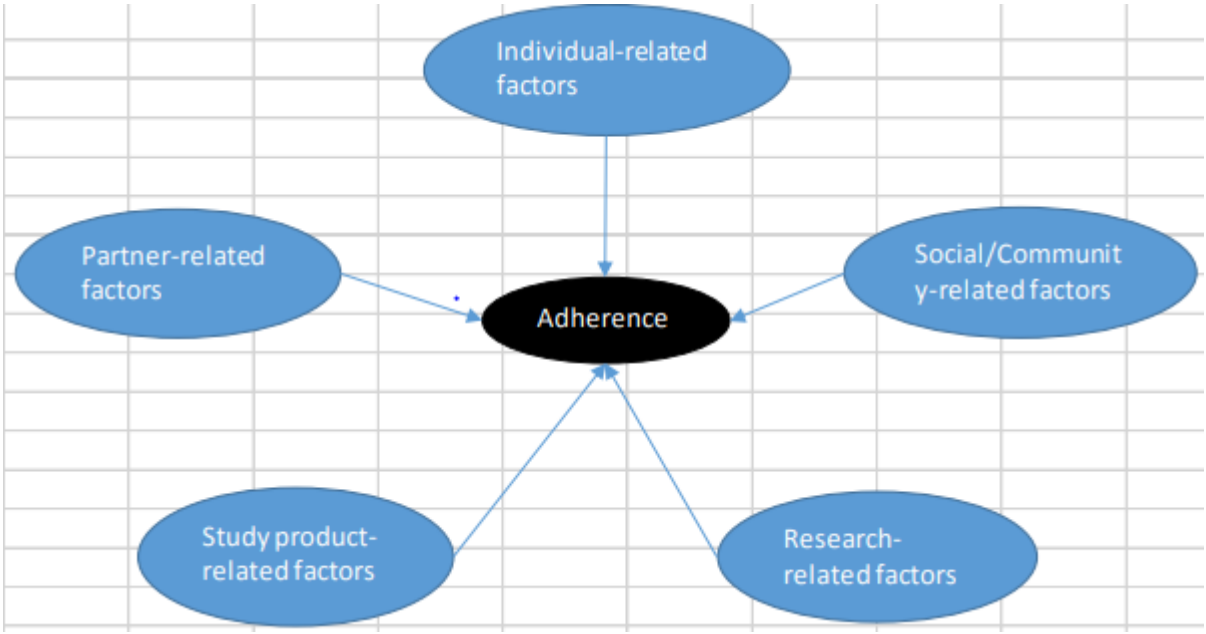

Figure 1. Conceptual Framework for Analysing Factors Affecting Adherence.

Results

Characteristics of Included Studies

Seventeen studies which were sub studies or ancillary studies of three out of four RCTs were retrieved, and as shown in Table 1, 12 of these studies which looked at factors affecting adherence, were included in this integrative review. The characteristics of the included studies are summarised in Table 1, 2 and 3. For the sake of completeness, the parent trials have been included, and the results of effectiveness assessment have been reported in a separate manuscript,[14] while those of adherence measurement will be reported separately. The PRISMA flow diagram is shown in Figure 2. Tables 2 and 3 show the study designs, the number of participants in the different studies, and the length of follow-up in the cohort studies. As shown in the tables, one study was a nested case-control study, three were purely qualitative, and 13 were cohort studies, five of which utilised mixed methods. The qualitative studies utilised in-depth interviews, ethnographic interviews and focus group discussions, making them extremely rich. Of these studies, 12 reported factors affecting adherence and were included in this study.

Risk of Bias Assessment/Evaluation

Risk of bias assessments for the included observational studies were made using the Newcastle-Ottawa Scale, and the results have been presented in Figures 3 and 4, whilst a Critical Skills Appraisal Programme (CASP) tool was used to assess the qualitative studies (Figure 5). Some of the studies employed mixed methods involving both qualitative and quantitative methods.

Table 1. Summary of Parent Studies and their Sub-studies

Primary Effectiveness Study		**Adherence Sub-studies**		
Intervention	Author, Year of Publication, Journal, Trial name	Author, Journal, Year of Publication	Adherence Measure ± Outcome	Factors affecting adherence
TFV gel versus Placebo	Karim et al., 2010, Science CAPRISA-004	Dellar et al, 2014, AIDS Behav	χ	√
		Gengiah et al, 2014, AIDS Behav	√	χ
		Matthews et al, 2013, PLoS ONE	√	√
		MacQueen et al, 2014, AIDS Behav	√	χ
		Mansoor et al, 2014, AIDS Behav	√	χ
		Succop et al, 2014, AIDS Care	χ	√
TDF versus Placebo	Peterson et al., 2007, PLoS Clinical Trials	--	--	--
TFV gel, TDF and TDF-FTC versus their placebo	Marrazzo et al., 2015, N Eng J Med VOICE	Van der Straten, 2016, JIAS	√	χ
		Van der Straten, 2014, PLoS ONE	χ	√
		Van der Straten, 2015, AIDS	χ	√
		Van der Straten et al, 2014, JIAS	χ	√
TDF-FTC versus placebo	Van Damme et al., 2012, N Eng J Med FEM-PrEP	Corneli et al, 2016, JAIDS	χ	√
		Corneli et al, 2014, JAIDS	χ	√
		Corneli et al, 2014, JIAS	χ	√
		Agot et al, 2015, AIDS Behav	√	χ
		Corneli et al, 2014, JAIDS	√	√
		Corneli et al, 2015, JAIDS	χ	√
		Corneli et al, 2015, PLoS ONE	χ	√

Table 2. Summary Characteristics of Observational Studies

Author, Year of Publication, Journal, Study name if applicable	**Location**	**Funding Source /Author declaration of financial interest**	**Study Design/ Parent Study**	**Number of Participants/ Follow-up**	**Study participants /Characteristics**
Corneli A et al, 2016, J Acquir Immune Defic Syndrome	Research sites in Bondo, Kenya and Pretoria, South Africa	USAID. No competing interests declared.	Cohort study. Mixed qualitative and quantitative methods. Parent study: FEM-PrEP	88 participants for qualitative semi-structured interviews (SSIs), 224 for quantitative audio computer-assisted self-interview (ACASI).	Mean age 24.2 years, median 23 years, range 18-35 years
Corneli A et al, 2014, J Acquir Immune Defic Syndrome	Sites in Bondo, Kenya and Bloemfontein and Pretoria, South Africa	USAID. No significant financial disclosures.	Prospective cohort. Parent study: FEM-PrEP	Bondo, n=50, Bloemfontein, n=50 and Pretoria, n=50.	Mean age 24.2 years, median 23 years, range 18-35 years.
Van der Straten A et al, 2016, Journal of the International AIDS Society	15 Clinical Research Sites in South Africa, Uganda and Zimbabwe	NIH. No significant conflicts of interests were disclosed.	Prospective cohort. Parent study: VOICE	N=472. Oral group: n=314, Vaginal group: n=158.	Mean age 25.4±5.2 years.
Corneli A et al, 2014, Journal of the International AIDS Society	Sites in Bondo, Kenya and Pretoria, South Africa	USAID. No conflicts of interest declared.	Cohort study. Mixed qualitative and quantitative methods. Parent study: FEM-PrEP	N=61 (Pretoria, n=34; Bondo, n=27)	40 participants < 25 years old, 21 participants ≥25 years old. 21% in Pretoria had >1 sexual partner, 41% in Bondo had >1 sexual partner.
Agot K et al, 2015, AIDS Behav	Sites in Bondo, Kenya and Bloemfontein and Pretoria, South Africa	USAID. No significant conflicts of interest were declared.	Prospective cohort study. Mixed qualitative and quantitative methods. Parent study: FEM-PrEP	N=150 (Bondo, n=50; Bloemfontein, n=50 and Pretoria, n=50).	Mean age 23.9 years. Median 23 years, range 18-35 years.
Corneli A et al, 2014, J Acquir Immune Defic	Sites in Bondo, Kenya and Bloemfontein	USAID. No competing financial	Prospective cohort study. Parent study: FEM-	N=150 (Bondo, n=50; Bloemfontein, n=50 and Pretoria, n=50)	Mean age 23.9 years. Median 23.0 years, range

Syndrome	and Pretoria, South Africa	interests disclosed.	PrEP.		18-35 years. 27% married.
Corneli AL et al, 2015, J Acquir Immune Defic Syndrome	Sites in Bondo, Kenya and Pretoria, South Africa	USAID. No conflicts of interest were declared.	Cohort study. Mixed qualitative and quantitative methods. Parent study: FEM-PrEP.	88 SSIs (Bondo, 43; Pretoria, 45). ACASI 224 (Bondo, 112 and Pretoria, 112).	Mean age 24.2 years, median 23 years, range 18-35 years).
Corneli A et al, 2015, PLoS ONE	Sites in Bondo, Kenya and Pretoria, South Africa	USAID. No conflicts of interest were declared.	Cohort study. Mixed qualitative and quantitative methods. Parent study: FEM-PrEP	88 SSIs (Bondo, 43; Pretoria, 45). ACASI 224 (Bondo, 112 and Pretoria, 112).	Mean age 24.2 years, median 23 years, range 18-35 years).
Dellar RC et al, 2014, AIDS Behav	2 CAPRISA clinics in KwaZulu-Natal, South Africa.	CAPRISA, USAID and FHI-360. No financial declarations statement was made.	Cohort study. Parent study: CAPRISA-004.	725 CAPRISA-004 participants.	Mean age 23.8±5.1 years.
Gengiah TN et al, 2014, AIDS Behav	2 CAPRISA clinics in KwaZulu-Natal, South Africa.	CAPRISA, USAID and FHI-360. No conflicts of interest were declared.	Cohort study. Parent study: CAPRISA-004.	889 CAPRISA-004 participants.	Mean age 23.8±5.1 years.
Matthews LT et al, 2013, PLoS ONE Pregnancy and adherence sub-study.	2 CAPRISA clinics in KwaZulu-Natal, South Africa.	CAPRISA, USAID and FHI-360. One author applied for a patent of the study product for another trial for its effect on herpes simplex 1 and 2 infections.	Prospective cohort study. Parent study: CAPRISA-004.	868 CAPRISA-004 participants.	Median age 22 years, range 20-26 years.
MacQueen KM et al, 2014, AIDS Behav	2 CAPRISA clinics in KwaZulu-Natal, South Africa.	USAID. No financial declarations statement was made.	Nested case-control study. Parent study: CAPRISA-004.	N=277 (Cases, 72; Controls, 205).	Mean ages: cases 22.7 years, controls 24.2 years. Range 18-40 years
Succop SM et al, 2014, AIDS Care	2 CAPRISA clinics in KwaZulu-Natal, South Africa.	USAID. No financial declarations statement was made.	Prospective cohort study. Mixed qualitative and quantitative methods. Parent study: CAPRISA-004.	N=277. CAPRISA-004 participants. 72 sero-converted during trial participation.	Mean ages: Seroconverters, 22.7 years. Non-seroconverters 24.2 years. Range 18-40 years.

None of the studies showed any significant risk of bias according to the Newcastle-Ottawa scale for studies which utilised quantitative methods, and all the qualitative studies or qualitative components of mixed studies were of good quality as shown in these risk of bias assessments (evaluation) figures.

Synthesis

Themes were extracted into the individual level factors, partner related factors, social/community related factors, product related factors and research related factors.

Individual Level Factors

Corneli et al[15] and van der Straten et al.,[17,18] identified high-risk perception as a facilitator of adherence. Those with preventive misconception regarding the study reported better adherence than those who felt protected by condoms.[16,19] Conversely, those who felt they were on the placebo and not protected reported reduced adherence.[19] False sense of low-risk can arise from serial negative tests and facilitate preventive misconception.[16] Knowing a partner's negative HIV status based on previous tests was reported by some to reduce product use.[16] Matthews et al. found that participants who had a desire to conceive adhered less to the study gel.[20]

Fear of side effects and not wanting to take tablets when not sick were recurring themes.[17,18,21] These side effects could be real, perceived or undesirable experiences. Logistical considerations were identified for travellers and social functions/places, whilst others reported

Table 3. Summary Characteristics of Included Qualitative Studies

Author, Year of publication, Journal, Study name	Location	Funding Source/ Author declaration of financial interest	Study Design / Parent study	Number of participants	Study Participants Characteristics
Van der Straten A et al., 2014, *PLoS ONE* VOICE-C	Clinical Research Site in Johannesburg, South Africa	NIH. No competing financial interests were declared.	Qualitative study (with In-depth interviews (IDI), Ethnographic Interviews (EI) and Focus group discussions (FGD)). Parent study: VOICE	N=102 (41 IDI, 21 EI and 40 FGD)	Mean age 26.8 years, range 19-40 years.
Van der Straten A et al., 2015, *AIDS* VOICE-D	Clinical Research Sites in Kampala, Uganda; Durban, South Africa and Chitungwiza, Zimbabwe	NIH. No significant financial interests were declared.	Two-stage qualitative study (multi-centre, ancillary study). Parent study: VOICE.	131 enrolled, 127 interviewed: IDIs only, n=55; Both IDIs and FGDs, n=13 and FGDs only, n=59. All were VOICE participants.	Age: mean 29.3 years, median 28 years, range 21-41 years. Number of lifetime partners: mean 11.8, median 3, range, 1 to >99.
Van der Straten A et al., 2014, *Journal of the International AIDS Society* VOICE-C	Johannesburg, South Africa	NIH. No conflicts of interest were declared.	Exploratory ancillary qualitative study. Parent study: VOICE.	N=102 (other participants not reported here are 22 male partners and 40 community members).	Mean age 26.8 years, range 19-40 years.

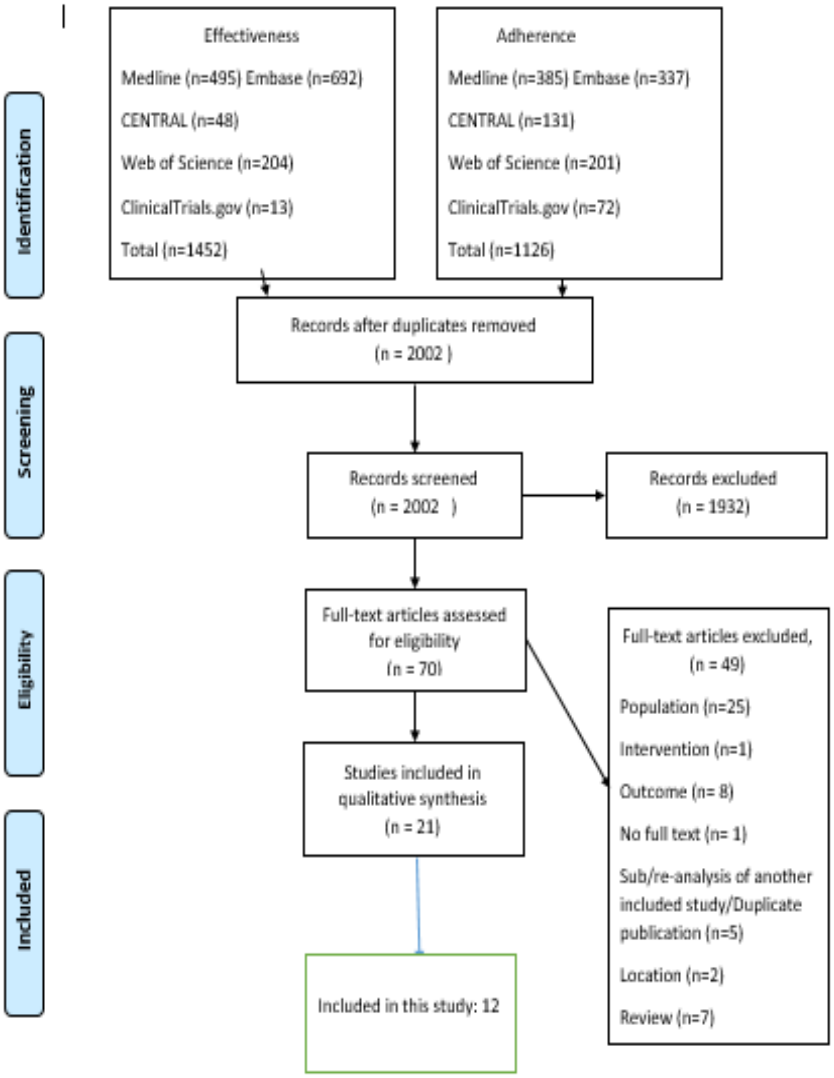

Figure 2. PRISMA Flow Diagram.

	Criterion	Corneli et al, 2016, JAIDS	Corneli et al, 2014, JAIDS	Van der Straten et al, 2016, JIAS	Corneli et al, 2014, JIAS	Agot et al, 2015, AIDS Behav	Corneli et al, 2014, JAIDS	Corneli et al, 2015, JAIDS	Corneli et al, 2015, PLoS ONE	Dellar et al, 2014, AIDS Behav	Gengiah et al, 2014, AIDS Behav	Matthews et al, 2013, PLoS ONE	Succop et al, 2014, AIDS Care
A	**Selection**												
	Representativeness of the exposed cohort	★	★	★	★	★	★	☆	☆	★	★	★	★
	Selection of the non-exposed cohort	☆	☆	★	★	☆	★	☆	☆	★	☆	★	☆
	Ascertainment of exposure	★	★	★	★	★	★	★	★	★	★	★	★
	Demonstration that outcome of interest was not present at start	★	★	★	★	★	★	★	★	★	★	★	★
B	**Comparability**												
	Comparability of cohorts on the basis of design or analysis	☆	☆	★	★	★	★	☆	☆	☆	★	★	☆
C	**Outcome**												
	Assessment of outcome	★	★	★	★	★	★	★	★	★	★	★	★
	Was follow-up long enough for outcomes to occur	★	★	★	★	★	★	★	★	★	★	★	★
	Adequacy of follow-up of cohorts	★	★	★	★	★	★	★	★	★	★	★	★
D	**Overall score**	6	6	8	8	7	8	5	5	7	7	8	6

Figure 3. Newcastle-Ottawa Scale for Cohort Studies.

forgetfulness.[21] Motivation for joining clinical trials also recurred several times. Some joined solely for financial and clinical benefits,[17,22] including monthly reimbursements. Yet, others reported strong internal motivation, including obligation to research, wanting to contribute towards positive outcomes, protecting themselves and future generations.[17,22]

Partner Support

Partner approval or disapproval and disclosure emerged as key themes.[18,21-23] Those who disclosed to supportive partners reported better adherence. Supportive partners reminded study participants to use their products and attend study visits. However, some did not give permission to their partners to use the products due to lack of understanding and fear of side effects. Those who had disclosed to their partners, found it easy to use study products in their presence or when they visited unexpectedly whereas those who had not disclosed study products, found it challenging to use them in their presence.

Social and Community Level Factors

Community discouragement, rumours, myths and misconceptions emerged commonly as themes for non-adherence.[17,18,21] Some cited being told that they were being exploited or being given harmful drugs. Fear of stigmatisation that they were HIV positive in communities where stigma surrounding HIV is still rife was commonly cited, as people knew that ARVs were drugs for HIV treatment and did not understand using them for prevention.[18,21] Some modified their regimens to suit their social and sexual lifestyles resulting in inconsistent use.[17] Some wanted hiding places for their products and were not willing to carry them when they travelled.

Product Related Factors

Commonly cited was fear of side effects, experiencing side effects and disliking the colour or size of pills.[17,21,24,25] Some altered regimens, doses or stopped using products altogether.[17] Others used products around the time of visit to have detectable drug in their blood in order to remain in the study.[17] Yet, others adhered not for HIV prevention but for thinking that the drug would treat other ailments[22] whilst others reported improved sexual experiences with study products.[17]

	Criterion	MacQueen et al, 2014, AIDS Behav
A	**Selection**	
	Is the case definition adequate?	★
	Represantativeness of the cases	★
	Selection of controls	★
	Definition of controls	★
B	**Comparability**	
	Comparability of cases and controls on the basis of design or analysis	★
C	**Exposure**	
	Ascertainment of exposure	★
	Same method of ascertainment for cases and controls	★
	Non-response rate	★
D	**Overall score**	8

Figure 4. Newcastle-Ottawa Scale for Case-control Studies.

	Checklist item	Corneli et al, 2016, JAIS	Van der Straten et al, 2014, PLoS ONE	Corneli et al, 2014, PLoS ONE	Agot et al, 2015, AIDS Behav	Corneli et al, 2015, JAIDS	Corneli et al, 2015, PLoS ONE	Succop et al, 2014, AIDS Care	Van der Straten et al, 2015, AIDS	Van der Straten et al, 2014, JIAS
1	**Clear statement of research aims**	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	**Qualitative methodology appropriate**	✓	✓	✓	✓	✓	✓	✓	✓	✓
3	**Research design appropriate**	✓	✓	✗	✓	✓	✓	✓	✓	✓
4	**Recruitment strategy appropriate**	✓	✗	✓	✗	✓	✓	✓	✓	✗
5	**Data collected in a suitable way**	✓	✓	✓	✗	✓	✓	✓	✓	✓
6	**Relationship between researcher and participants adequately considered**	✓	✓	✓	✓	✓	✗	✗	✓	✓
7	**Ethical issues taken into consideration**	✓	✓	✓	✓	✓	✓	✓	✓	✓
8	**Data analysis sufficiently vigorous**	✓	✓	✓	✓	✓	✓	✓	✓	✓
9	**Clear statement of results**	✓	✓	✓	✓	✓	✓	✓	✓	✓
10	**Research is valuable**	✓	✓	✓	✓	✓	✓	✓	✓	✓

Figure 5. Critical Appraisal Skills Programme Tool for Qualitative Studies.

Research-related Factors

Themes emerged regarding trusting researchers and liking/disliking the research environment.[17,18,21,24] Mistrust of researchers' motives inhibited adherence whilst trust enhanced adherence.[17,18] Some participants did not like the idea of being on a placebo as they felt they were being experimented on.[18,24] This is while others liked the research environment and research staff, and liked the regular medical screening they got in the research clinics.[24] Good conduct and level of care from the research staff and treatments for other ailments facilitated study visits.

Discussion

We identified common themes and placed them within five categories based on a modification of Ickovics' and Meisler's conceptual framework.[13] Within each category, facilitators and barriers were placed, with no relative weights. The identified categories were individual -related, partner-related, social and community level, product-related and research-related factors.

Risk-perception and preventive misconception emerged as key themes.[15,18,19,21,22] Risk perception is the extent to which an individual perceives her chances of acquiring HIV whilst preventive misconception refers to the perceived protection from a product or a programme. High-risk perception promotes adherence to PrEP, and so does preventive misconception from a PrEP regimen.[22] Women who perceive better protection from other biomedical interventions such as condoms might not see the need to adhere to PrEP.[19]

Support or discouragement from the male partner was noted to enhance or reduce adherence to the products.[17,18,21-24] Because of the patriarchal nature of African societies, men still have a lot of influence regarding women's sexual and reproductive health decisions.[26,27] In the examined studies, disclosure of product use to the partners promoted adherence, whilst partial or non-disclosure resulted in challenges.[23] It is believed that involving male partners or sensitising them from the outset may help. However, this discussion is mainly based on results from qualitative studies, with limited generalisability to the general population as contexts vary. Partners' level of education and socio-economic status may be important determinants of product use, though this has not been formally evaluated.

Community themes fell into understanding of research, stigma around HIV/AIDS and rumours, myths and misconceptions.[17,18] In some African contexts ideas that emerge from Western countries may be perceived as exploitative, and given that most of the PrEP trials were western-funded, it was not surprising that the idea of being experimented on emerged. If population level PrEP roll-out is implemented by development partners, such issues will need to be addressed adequately for successful uptake. Communities must be adequately involved and sensitised, as this could help to dispel myths and misconceptions. Stigma regarding HIV/AIDS is still present in communities, and could dissuade women from using PrEP as they fear from being labelled.[18]

Several research-related themes emerged, which might not exist during population-level PrEP roll-out. These included a friendly research environment and supportive staff, which emerged as facilitators of adherence.[24] This is while there sometimes was discordance between reported and objectively measured adherence, as the study participants exaggerated adherence to increase social desirability. Regular medical check-ups and free access to medical services attracted research participants, and these will not be existent in the real world.[24]

Colour and size of pills mattered; with others reporting that, the pills might have been big and difficult to swallow.[25] Smaller pills or attractive colours might therefore promote adherence. It will be difficult to suit everybody as different experiences are reported with the same product. Furthermore, experienced or perceived side effects emerged as barriers to adherence.[17,18,21,28] In the past, antiretroviral drugs have been associated with nasty side effects including disfigurement. Some communities have had negative perceptions of ARVs over the past years. It is worth mentioning that implementers must be adequately prepared to deal with these issues.

Sub-studies nested within PrEP trials provided data regarding adherence profiles among different groups of participants. For qualitative studies, participants are purposively sampled to obtain rich qualitative data to answer research questions; however, outside their particular contexts, these results have limited generalisability. High levels of adherence to PrEP were noted in a study of sero-discordant couples in Uganda and Kenya.[29] In a qualitative sub-study of the same trial, high-risk perception by the negative partner was perceived to play an important role in adherence.[30]

After discovering the partner's positive status, one would go into a dilemma of staying or leaving and exhibited different reactions. When they decided to stay they were very aware of the possibility of being infected and could have perceived PrEP as a way of preventing infection. Preventive misconception might even be higher in the population of sero-discordant couples. Similar findings were noted in a sub-study of an oral PrEP clinical trial in Botswana, where there was a significant association between having an HIV positive partner and adherence to study pills.[31]

Across studies from different sites, countries and methodologies, comparable factors were noted to have an impact on adherence qualitatively and quantitatively. The broader socio-economic set up in SSA is comparable, with some regional differences. Knowledge gained in this study may be applied to these settings for better oral PrEP uptake.

Strengths

This integrative review hoped to inform future clinical trials and population-level sexual and reproductive health interventions to design best practices, aimed at improving clinical outcomes. Multiple databases were searched to ensure inclusion of all relevant literature, and thematic synthesis of factors affecting adherence to PrEP across different studies was done.

Limitations

Results noted during studies in a controlled environment do not necessarily apply outside the research environment. Biases stemming from social desirability imply that study participants may give responses they think are appropriate for the environment, and results from qualitative studies have limited generalisability outside the context of the study.

Implications for Public Health and Research

Researchers and public health stakeholders must adequately address barriers to adherence in future studies to ensure maximum adherence and optimal uptake of such useful public health interventions.

Conclusion

Significant barriers and facilitators of PrEP uptake were identified and categorised in this study based on a modification of Ickovics and Meisler's conceptual framework. Researchers and public health stakeholders must fully understand these factors as they embark on future research, to ensure promotion of facilitators of PrEP uptake, and addressing barriers adequately. This will optimise uptake of public health interventions for realisation of maximal benefits.

Authors' Contributions

GM identified the concept, performed literature search, screened articles for eligibility, and developed the primary manuscript. He critically revised, read, finalised and decided to submit the final manuscript for publication.

Conflict of Interest

The author declares no conflicts of interest.

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