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REVIEW

Adherence and Compliance with Oral Pre-Exposure Prophylaxis (PrEP) for HIV Prevention

Adherencia y cumplimiento de la Profilaxis Pre Exposición (PrEP) para la prevención del VIH

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ABSTRACT

Introduction: men who have sex with men (MSM), transgender people, sex workers, people who inject drugs, individuals in prisons and other closed settings have been considered key populations because they are at high risk of contracting HIV. The World Health Organization (WHO) has recommended Oral Pre-Exposure Prophylaxis (PrEP) because of its protective effect against HIV in this population. This study aims to analyze the factors that influence adherence and compliance with oral PrEP for HIV prevention.
Method: this systematic review was conducted the databases used were the PubMed, CINAHL Complete, and EMBASE. For search keywords, MeSH, CINAHL Subjects, and Emtree terms were combined with AND and OR Boolean operators. Studies selected encompassed quantitative, qualitative, mixed, and multimethod designs, between from 2015 to 2022, in English, Spanish, and Portuguese language. All references were imported and exported through EndNote for data collection. Methodological quality was evaluated using the MMAT checklist. We used deductive thematic analysis based on Taylor there are six categories that influence adherence and compliance to oral PrEP.
Results: out of 526 articles retrieved, 314 duplicates were eliminated and 26 were incorporated. Various factors affect adherence and compliance with oral PrEP.
Conclusions: based on the findings, PrEP's effectiveness and the perceived high risk of HIV infection served as motivators for PrEP utilization, while negative sentiments regarding PrEP, side effects, and stigma acted as hurdles to its use. Readiness facilitated PrEP adoption. Healthcare team support was viewed as an effective attribute for those administering oral PrEP.

Keywords: Adult; Human Immunodeficiency Virus; Pre-Exposure Prophylaxis; Treatment Adherence and Compliance; Systematic Review.

RESUMEN

Introducción: los hombres que tienen relaciones sexuales con hombres (HSH), las personas transexuales, trabajadores sexuales, las personas que se inyectan drogas, los individuos privados de libertad y otros entornos cerrados se han considerado poblaciones clave por su alto riesgo de contraer el VIH. La Organización Mundial de la Salud (OMS) ha recomendado la PrEP por su efecto protector frente al VIH en esta población. Este estudio pretende analizar los factores que influyen en la adherencia y el cumplimiento de la Profilaxis Pre Exposición (PrEP) oral para la prevención del VIH.

Método: se realizó esta revisión sistemática las bases de datos utilizadas fueron PubMed, CINAHL Complete y EMBASE. Para la búsqueda de palabras clave, se combinaron los términos MeSH, CINAHL Subjects y Emtree con los operadores booleanos AND y OR. Los estudios seleccionados abarcaron diseños cuantitativos, cualitativos, mixtos y multi método, entre 2015 y 2022, en idioma inglés, español y portugués. Todas las referencias fueron importadas y exportadas a través de *EndNote* para la recolección de datos. La calidad metodológica se evaluó mediante la lista de verificación MMAT. Se utilizó un análisis temático deductivo basado en Taylor hay seis categorías que influyen en la adherencia y el cumplimiento de la PrEP oral.
Resultados: de los 526 artículos recuperados, se eliminaron 314 duplicados y se incorporaron 26. Diversos factores influyen en la adherencia y el cumplimiento de la PrEP oral.
Conclusiones: según los resultados, la eficacia de la PrEP y el alto riesgo percibido de infección por VIH sirvieron como motivadores para la utilización de la PrEP, mientras que los sentimientos negativos respecto a la PrEP, los efectos secundarios y el estigma actuaron como obstáculos para su uso. La disposición facilitó la adopción de la PrEP. El apoyo del equipo sanitario se consideró un atributo eficaz para quienes administran la PrEP oral.

Palabras clave: Adulto; Virus de Inmunodeficiencia Humana; Profilaxis Pre-Exposición; Adherencia y Cumplimiento del Tratamiento; Revisión Sistemática.

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is a significant public health concern worldwide. In 2022, the Joint United Nations Programme on HIV/AIDS reported 38,4 million individuals living with HIV globally along with 1,5 million new HIV infections, concentrated in key populations. In 2019, there was a surge in new HIV infections, amounting to 62 % [1] globally and 21 % in Latin America among key populations.[2]

According to the World Health Organization (WHO), key populations are groups that are at a higher risk of HIV infection and include men who have sex with men (MSM), people who inject drugs (PWID), people in detention and other closed settings, sex workers, and transgender people.[3]

To combat the spread of HIV, the global response recommends combination prevention,[4] a strategy that employs multiple interventions, including oral pre-exposure prophylaxis (PrEP). The PrEP is a prevention strategy that uses the antiretroviral combination of tenofovir disoproxil fumarate and emtricitabine or lamivudine and consists of daily consumption of this drug prior to sexual activity. One study showed that daily use of PrEP prevents HIV acquisition[5] or taking four or more doses of PrEP per week reduces the risk of infection by 99 % [4,6], particularly in key populations.[7,8,9,10,11] According to WHO, in 2015 this intervention was suggested for this population[5] and by 2023, a total of 60 countries have incorporated PrEP in their health system.[12]

Adherence is defined as the behavior of the person to follow a given treatment and compliance as the coincidence between the patient's behavior and the medical prescription. As a worldwide strategy, oral PrEP monitoring has been recommended.[12] Currently, adherence and compliance can be assessed and measured by means of self-report questionnaires.[13] There are other adherence metrics including pharmacological (hair, urine), electronic adherence monitors, pharmacy refills, electronic pill intake and pill counts, however, self-reporting has been shown to have some advantages as a tool for use in professional care and cost-effectiveness.[14]

According to Taylor et al. there are six categories that influence adherence and compliance to oral PrEP in the patient such as: 1) motivations to use PrEP, 2) barriers to PrEP use, 3) facilitators to PrEP use, 4) sexual decision making in the context of PrEP, 5) prospective content of PrEP education, and 6) perceived effective characteristics of the staff administering oral PrEP.[15]

Adherence and compliance are relevant aspects in the effectiveness and efficiency of the treatment planned by the health professional. Despite the above, some studies have shown adherence levels ranging from 40 to 60 % in countries such as the United States, Uganda, and Brazil, respectively,[16,17,18] the latter showing 60 % adherence among MSM and transgender women.[14]

Since 2015, systematic reviews have been developed, however, with focus on MSM,[19,20,21,22] people who use injectable drugs,[23] transgender,[24] more than one key population,[25] only one review addressed MSM, people who use injectable drugs, transgender, people deprived of liberty and sex workers, but dates from 2018, which represents that adherence and compliance should be studied again due to lack of updated evidence. In this context, it is relevant to analyze the aspects that influence adherence and adherence to oral PrEP for HIV prevention.

METHOD

Study design

This was a systematic review of the aspects that influence adherence and compliance to oral PrEP and

was conducted following the "preferred reporting items for systematic review and meta-analyses" PRISMA: 1) formulation of the research question; 2) search strategy; 3) eligibility criteria; 4) selection of articles, 5) evaluation of the methodological quality of the studies and 6) synthesis and levels of evidence and reported by means of the Prisma Checklist.[26]

Formulation of the research question

The research question was what are the aspects that influence adherence and compliance to oral pre-exposure prophylaxis for HIV prevention? and formulated using the acronym PICO, where P: Population, I: Intervention, C: Comparison, O: Outcome.

Search strategy

The electronic databases US National Library of Medicine National Institutes of Health (PubMed), CINAHL Complete and Excerpta Medica Database (EMBASE) were used for the search, according to the recommendation of the Cochrane Collaboration,[27] as they represent the largest databases of peer-reviewed articles.

The strategy used for the PubMed database was a combination of Medical Subject Headings (MESH) descriptors, keywords, and Boolean operators. The search is shown in table 1:

Table 1. Strategy search used for the PubMed database

MeSH descriptors	Keywords	Boolean operators
HIV	Human Immunodeficiency Virus; Immunodeficiency Virus, Human; Immunodeficiency Viruses, Human, Virus; Human Immunodeficiency, Viruses; Human Immunodeficiency; Human Immunodeficiency Viruses; Human T Cell Lymphotropic Virus Type III; Human T-Cell Lymphotropic Virus Type III; Human T-Cell Leukemia Virus Type III; Human T Cell Leukemia Virus Type III; LAV-HTLV- III; Lymphadenopathy-Associated Virus; Lymphadenopathy-Associated Virus; Lymphadenopathy-Associated Viruses, Virus; Lymphadenopathy-Associated, Viruses Lymphadenopathy-Associated, Human T Lymphotropic Virus Type III; Human T- Lymphotropic Virus Type III; AIDS Virus; AIDS Viruses, Virus; AIDS Viruses; AIDS Viruses; AIDS, Acquired Immune Deficiency Syndrome Virus; Acquired Immunodeficiency Syndrome Virus; HTLV-III.	AND
Pre Exposure Prophylaxis;	Pre-Exposure Prophylaxi; Prophylaxi, Pre-Exposure; Prophylaxis, Pre-Exposure; Pre-Exposure Prophylaxis (PrEP); Pre Exposure Prophylaxis (PrEP); Pre-Exposure Prophylaxi (PrEP); Prophylaxi, Pre-Exposure (PrEP); Prophylaxis, Pre-Exposure (PrEP).	AND
Treatment Adherence and Compliance.	Therapeutic Adherence and Compliance; Treatment Adherence; Adherence, Treatment; Therapeutic Adherence; Adherence, Therapeutic.	AND

Eligibility Criteria

Quantitative, qualitative, mixed, and multi-method primary studies, published between 2015 to 2022, in English, Portuguese and Spanish language, about oral PrEP (tenofovir disoproxil fumarate and emtricitabine or lamivudine) were included.

Article selection

All references were imported into the EndNote bibliographic manager, likewise duplicates were eliminated by this manager and the literature was exported in RTF format to an Excel spreadsheet for the selection process that included reading title, abstract and complete. Discrepancies were discussed by one author.

Evaluation of the methodological quality of the included studies

The methodological quality of the included studies was assessed using the criteria of the Mixed Methods Appraisal Tool (MMAT) checklist,[28,29,30] which is a tool designed to simultaneously assess and describe the methodological quality of qualitative, quantitative (randomized, nonrandomized, and descriptive) and mixed methods studies.[28,29,30]

For the evaluation of the studies, the information of the articles to be evaluated must be entered, answer the questions to assess the eligibility of the articles, select the appropriate category of studies according to design (qualitative study, randomized clinical studies, non-randomized studies, descriptive quantitative studies, mixed methods studies) and finally score the studies according to the criteria "Yes" or "No" and "Can´t tell", the latter meaning that the document does not provide adequate information to answer "Yes" or "No", or that they report unclear information related to the criterion.[28,29,30]

Synthesis and level of evidence

For the synthesis of the information, the following data were extracted: author, country, participant inclusion criteria, sample size or number of participants, type of study, type of design, measurement instrument, findings, aspects that influence adherence and compliance.

Finally, the descriptive analysis was performed by means of percentages of the variables studied. The deductive thematic analysis was performed by means of the following stages: 1) familiarization with the data, 2) generation of initial codes, 3) search by themes, 4) review of themes, 5) definition of themes, and 6) articulation of themes with literature in the area and production of the final analysis.[31] The categories identified were grouped according to 1) motivations for using PrEP, 2) barriers to PrEP use, 3) facilitators to PrEP use, 4) sexual decision making in the context of PrEP, 5) prospective content of PrEP education, and 6) perceived effective characteristics of personnel administering PrEP.[15]

RESULTS

From a total of 526 articles identified, 59 were selected by title, 36 by title/abstract, 33 by full reading, and 26 were included.

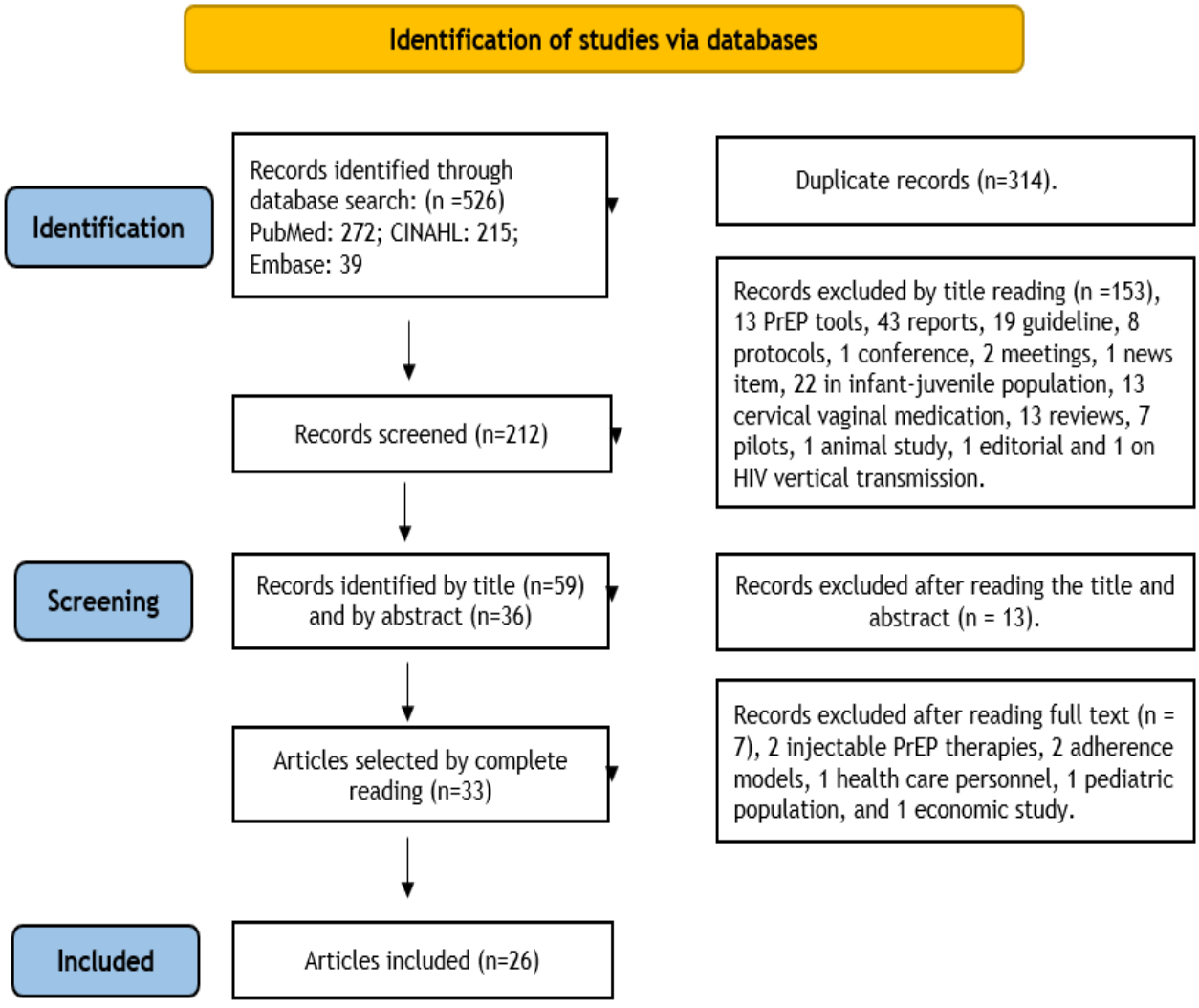

Figure 1. Flowchart on item selection process according to Prisma

Table 2. Characteristics of quantitative included studies

Author and country	Participants and sample	Type of study and design	Measurement	Motivations	Facilitators	Sexual decision making in the context of PrEP	Prospective content of PrEP education	Perceived effective characteristics of staff administering PrEP	Barriers
Closson et al.[32] United States	MSM black and TGW (n=79)	Quantitative randomized clinical trial	WAS of 3 items, PKQ of 13 items, AQ of 24 items, and PBBQ of 22 items	Were not identified	Were not identified	Were not identified	Were not identified	Were not identified	Low education (aOR 0,25, 95 % CI 0,13-0,49)
Ferrer et al.[33] Spain	MSM, aged 18 years and older, receiving care at WGP (n=472)	Quantitative survey	SSHS of 46 items	Were not identified	Willingness to use PrEP (32,6 %) Perceived ease of use of PrEP	Were not identified	Were not identified	Cost, facilitated the acceptability of PrEP	Were not identified
Fuchs et al.[34] United States	Transgender men and women who have sex with men (n=56)	Quantitative cohort	Weekly two-way text messages (iText) or weekly e-mail support messages for three months	Were not identified	Were not identified	Were not identified	The messages (iText) showed a 50 % reduction in missed doses (95 % CI: 16-71); p=0,008), also a reduction in the proportion of missed doses 77 % (95 % CI: 33-92); p=0,007, a reduction in self-reporting before each visit (p=0,11) and increase in the proportion of medication possession (27,8 %)	Were not identified	Were not identified
Hojilla et al.[35] United States	MSM, PrEP prescription, with known risk factors such as STIs, condomless sex, drug use (n=344)	Quantitative cohort	Clinical self-report questionnaires on sexual risk behavior in the last 12 months	Were not identified	Were not identified	Were not identified	Were not identified	78 % of those who received support from health personnel started PrEP	The perceived low protection of oral PrEP against STIs, whereby, men with STIs were 44 % less likely to be retained aOR: 0,56; (95 % CI: 0,33-0,95)

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Hu et al.[43] China	MSM (n=411)	Quantitative longitudinal	Adherence self-report and dichotomous scale on HIV-related characteristics with 13 questions and 11 items.	The effectiveness of PrEP (p<0,0001)	Marital status (divorced) (p<0,0001)	Were not identified	Were not identified	Were not identified	Were not identified
Koss et al.[36] Kenya and Uganda	Over 15 years of age, from rural Kenya and Uganda (n=3,466)	Quantitative longitudinal	Clinical assessment of PrEP uptake within 90 days of HIV testing, attendance at the follow-up visit at week 4, week 12 and every 12 weeks, refills, self-reported adherence through 72 weeks, and tenofovir concentrations in hair sample	Perception of high risk of HIV infection aOR=12,36; (95 % CI: 9,39-16,28); p<0,0001	Marital status separated, divorced or single aOR: 2,10; (95 % CI: 1,12-3,95); p=0,021	Were not identified	Serodiscordant couples aOR:1,64; (95 % CI: 1,22- 2,19); p= 0,0009	Were not identified	Were not identified
Kwan et al.[37] United States	Males, MSM, over 18 years of age, residents of Hong Kong (n=444)	Quantitative cross-sectional	Sociodemographic and clinical questionnaire and 14-item body image type instrument	High perceived risk of HIV infection Patients seeking sexual partners OR: 3,4 (95 % CI: 1,17-10,21); p= 0,03. Patients without HIV testing and in search of a partner OR: 2,97; (95 % CI: 1,23-7,16); p= 0,01	Were not identified	Were not identified	Were not identified	Were not identified	The low socioeconomic level (monthly income ≧ HK$10,000 USD$1,200 approx. OR: 2,48; (95 % CI: 1,21-5,08); p=0,01)
Lim et al.[38] Malaysia	Males (sex at birth), Malaysian citizen, over 18 years of age, MSM and be HIV negative or unknown status unknown (n=990)	Quantitative survey	Questionnaire Sociodemographic and clinical, likert-type scale to measure participants' attitudes regarding their perceived likelihood of contracting HIV. perceived likelihood of contracting HIV, short version of the seven-item willingness to use PrEP scale and another short five-item scale developed by the authors to complement the willingness to use PrEP and open-ended questions on access to and provision of PrEP services and dosing strategies according to preference	Perceived high risk of HIV infection aOR:1,36; (CI= 1,02-1,81); p= 0,036	Individuals with knowledge about PrEP aOR:1,40; (CI 95 %:1,06-1,86); p=0,018)	>2 male anal sex partners aOR:1,98; (95 % CI: 1,29-3,05); p=0,002	Were not identified	Were not identified	Malay ethnicity aOR: 1,73; (CI95 %: 1,12-2,70); p= 0,015

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Martin et al.[39] United States	Tenofovir Bangkok Project (BTS) participants who were non-pregnant, non-breastfeeding, HIV-negative, and current or former injection drug users at the time of BTS enrollment (n=2,306)	Quantitative randomized clinical trial	Evaluation of adverse effects, adherence and risk counseling, HIV antibody levels	Perceived high risk of HIV infection (injectable heroin use) aOR: 1,5, (95 % CI:1,1-2,1); p=0,007 and deprived of liberty aOR= 1,7, (95 % CI:1,3-2,1); p<0,0001 were predictors of PrEP initiation, patients using injectable heroin aOR: 3,0, (95 % CI:1,3-7,3); p= 0,01 and patients who were in prison aOR= 2,3, (95 % CI:1,4-3,7); p= 0,0007 were predictors of return for at least one follow-up visit. In addition, male patients aOR:1,9; (95 % CI: 1,0-3,6); p= 0,04), using injectable midazolam aOR: 2,2; 95 % CI:1,2-4,3); p= 0,02 and patients who were in prison aOR: 4,7; (95 % CI: 3,1- 7,2); p<0,0001 were predictors of > 90 % PrEP adherence in patients with follow-up visits	Were not identified	Were not identified	Were not identified	Were not identified	The age group (between 30 and 59 years) aOR: 1,8; (95 % CI: 1,4-2,2); p<0,0001)
Muwonge et al.[57] Kenya and Uganda	Couples, over 18 years of age and sexually active (n=142)	Quantitative Mixed	Sociodemographic questionnaire Interviews based on gender, age, and change reporting with brief message services, PrEP adherence counseling, and risk reduction counseling	Willingness to use PrEP (male condom) (p<0,001), a period longer than six months (p<0,001) and patients with incentive to participate in the study (p<0,001)	Were not identified	Were not identified	78 % of patients indicated that the text messaging service helped to remember to take PrEP	Were not identified	Were not identified
Salinas-Rodríguez et al.[40] México	Older than 18 years, male sex, self-reported sexual penetration or anal sex in the last six months with at least eight men, self-reported exchange of money, drugs, alcohol or gifts for sex at least 8 times in the last six months, negative HIV test in the last six months, literacy in Spanish speaking language (n=200)	Quantitative survey	Sociodemographic and clinical questionnaire	Coverage of the cost of PrEP	Were not identified	Were not identified	The hair test (ß= 1,7, (95 % CI 0,1-3,4), p=0,04	Were not identified	Were not identified

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Ssuna et al.[56] Uganda	Over 18 years old, residents of Ggaba (n=283), participants (quantitative phase), 16 participants (qualitative phase).	Quantitative mixed sequential exploratory	Sociodemographic and clinical questionnaire. Semi-structured interview with open-ended questions. PrEP acceptability dichotomous self-report. Focus groups to discuss acceptability and perception of PrEP	Willingness to use PrEP was associated with perceived high risk of HIV aOR:1,99, (95 % CI:1,31-3,02), p=0,001, having been tested for HIV in the past 6 months aOR: 1,13, (95 % CI 1,03-1,24), p=0,007, and completion of tertiary studies aOR:1,97, (95 % CI:1,39-2,81), p<0,001. HIV preventive	Were not identified	Were not identified	Were not identified	Were not identified	Drug dosage, PrEP side effects
Sun et al.[41] China	Male sex (at birth), older than 18 years, at least one anal intercourse without a condom in the last six months, self-reported HIV-negative or unknown serostatus, willingness to self-administer an HIV self-test (n=622)	Quantitative cross sectional	CSES of 6 items, CBSAMIS, PKS of 8 items. Sociodemographic and clinical questionnaire	Migrant patients aOR: 2,01; 95 % CI: 1,38-2,92); p<0,0001, sexual risk behavior aOR: 4,19; (95 % CI: 1,82-11,43); p=0,002), sex under the influence of drugs in the last six months aOR:2,57; (95 % CI: 1,67-4,03); p<0,001, people who did not have HIV prevention behavior aOR: 6,17; (95 % CI: 1,98- 27,40); p=0,005, were predictors of readiness for PrEP use.	Were not identified	Were not identified	Were not identified	Were not identified	Concealment of sexual orientation (aOR= 0,83; CI=0,70-0,96; p<0,015), having taken an HIV test in the past six months aOR:0,50; (95 % CI:0,34-0,74); p<0,001 and using text messaging (WeChat) for HIV prevention aOR: 0,84; (95 % CI:0,72-0,98); p<0,032, were factors negatively associated with willingness to take PrEP
Whiteley et al.[42] United States	MSM, predominantly black, aged 18-35 years, in newly initiated PrEP care at an affiliated clinic, aware of their HIV status, literate in English language (n=43)	Quantitative Cross-sectional derived from a randomized clinical trial	WAS of 3 items, HIV knowledge scale of 5 items, Information- MBS of 9 items, SSP of 5 items, ICCCU of 1 item, GSIBSI of 18 items, SRB of 6 items, Alcohol, tobacco and substance use screening (ASSIST) of 5 items.	Participants who are more likely to adhere to PrEP are those who reported a sexual partner around the time in the initial phase of the study aOR: 8,3; (95 % CI: 0,99-69,54), p= 0,05. In addition, patients presenting self-efficacy of aOR adherence: 19,96; (95 % CI: 1,43-225,15), p= 0,03)	Were not identified	Were not identified	Were not identified	Were not identified	Were not identified

Source: HIV= Human Immunodeficiency Virus; MSM= Men who have Sex with Men; CI= Confidence Interval; p: p-value; aOR= Adjusted Odds Ratio; OR: Odds Ratio; RRa= Adjusted Risk Ratio; WAS= Wilson Adherence Scale; PKQ=PrEP Knowledge Questionnaire; AQ=Attitude Questionnaire; PBBQ= Perception of Benefits and Barriers Questionnaire; TW= Transgender Woman; WGP= World Gay Pride; SSHS= Spanish Sexual Health Survey; STIs= Sexually Transmitted Infections; HK= Hong kong Dollar; USD= United States Dollar; BTS= Bangkok Project; CSES= Condom Use Self Efficacy Scale; CBSAMIS= Concealment Behavior Scale on American Men's Internet Survey; GSIBSI=Global Severity Index of the Brief Symptom Inventory; SRB= Sexual risk behavior, PKS= PrEP Knowlegde Scale; MBS= Motivation- Behavioral Skills; SSP= Social Support for PrEP; ICCCU= Importance of Condom and Confidence in Condom Use.

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Table 3. Characteristics of the included qualitative studies

Author and country	Participants and sample	Type of study and design	Measurement instrument	Motivations	Facilitators	Sexual decision making in the context of PrEP	Prospective content of PrEP education	Perceived effective characteristics of staff administering PrEP	Barriers
Alt et al.[52] United States	Self-identified cisgender gay or bisexual cisgender men (n=14)	Qualitative Consensual	Semi-structured interview	Were not identified	Participants described having good knowledge about PrEP, prior to starting therapy and acquired through social networks, television, internet or other digital media	Were not identified	Were not identified	Were not identified	Participants identified some obstacles to maintaining the required doses. Experiences of internalized homophobia and related stigma may affect the decision to take PrEP. Participants presented discomfort when discussing their sexual activity with the medical professional
Cahill et al.[54] United States	Transgender women, who have sex with men, HIV negative, having had at least one episode of insertive or receptive anal sex in the last three months (2 groups (n=11 and n=8).	Case study	Focus group	Were not identified	Were not identified	Were not identified	Were not identified	Were not identified	PrEP side effects, socioeconomic status (poverty), and dissatisfaction with medical care
Chemnasiri et al.[53] Thailand	MSM, aged 21-50 years, on PrEP therapy (n=32)	Qualitative Grounded Theory	Semi-structured interview and focus group	Were not identified	The use of strategies to obtain PrEP, availability of therapy, simplicity of requirements and PrEP regimen according to personal characteristics	Were not identified	Were not identified	Were not identified	Perception of low HIV risk, difficulties adhering to regimens in case of intoxication, concern about side effects, experience of HIV stigma, and affordability of PrEP outside the study setting influencing acceptance and use in the community
Franks et al.[55] United States	MSM, transgender women, women who have sex with men (n=37)	Quantitative descriptive	Focus group of 20 questions and semi-structured interview of 19 questions	Were not identified	Were not identified	Were not identified	Were not identified	Were not identified	Stigma

Liu et al.[44] China	MSM, over 18 years of age, self-identified as a biological male, had oral and/or anal sex with a man in the last 6 months, have a negative HIV test result (n=32)	Qualitative. Descriptive	Semi-structured interview and audio recording on perceived HIV risk, prior knowledge of PrEP, perceived barriers and facilitators to PrEP uptake, main male partner attitudes toward PrEP, convenience and comfort of PrEP (vs. condom use) PrEP. to PrEP uptake, main male partner attitudes towards PrEP, convenience, and comfort of PrEP (vs. condom use) PrEP	Were not identified	Were not identified	Perceived high risk of HIV, beliefs about the efficacy of PrEP, and concern about transmitting HIV to others were the reasons for PrEP uptake adherence and access	Were not identified	Distrust of the national PrEP program	Perception of low HIV risk, and concern about side effects were the reasons for not wanting to use PrEP. Lack of support from the primary sexual partner, difficulties in complying with the daily drug regimen, and schedules were the reasons for not wanting to use or stop using PrEP
Longino et al.[45] Perú	MSM, transgender women and sex workers. 38 patients divided into two groups of 18 and 20 patients, respectively	Qualitative Descriptive	Semi-structured interview and focus group	Elevated risk due to sex work and sexual/ gender identity and the promise of PrEP for their specific communities were aspects that increase PrEP use and adherence	Were not identified	Were not identified	Were not identified	Were not identified	Concern about the safety of the drug, concern about the financial advantage of the therapy for the pharmaceutical company. Concerns about the motives of the pharmaceutical company with respect to costs and access to the drug
Ngure et al.[46] Kenya	Heterosexual HIV serodiscordant couples, MSM and at-risk women aged 20-57 years. 40 people (20 couples)	Qualitative Descriptive	The resumption of a normal life, the significance of PrEP as additional HIV protection provided by PrEP, the first experiences of PrEP that reinforces its use, were aspects that facilitate the initiation and continuation of PrEP	Were not identified	Were not identified	Were not identified	Were not identified	Were not identified	Were not identified
Owens et al.[47] United States	Cisgender or transgender men who have sex with men, 18 years of age or older, currently	Qualitative Data Driven Theory	Online interviews recorded via Facebook and twitter	Participants were motivated to adhere to prevent HIV acquisition and be financially responsible.	Were not identified	Were not identified	Were not identified	Were not identified	Future communication about PrEP adherence between patient and provider varied among participants

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	prescribed PrEP and living in rural areas in midwestern states of the United States (n=34)			All participants (n=34) mentioned that the health professional discussed the importance of adherence with the effectiveness of PrEP					
Sevelius et al.[48] United States	Over 18 years of age, sexually active within the last three months, assigned male at birth and reported with gender identity as female, transgender women, or others who do not identify as male (n=30)	Qualitative Descriptive	Focus group and interviews	Access to a competent health professional, low power to negotiate safe sex, and risk perception were facilitators of PrEP acceptance	Were not identified	Were not identified	Were not identified	Were not identified	Non-trans-inclusive PrEP advertising, PrEP interaction with hormone therapy, multiple drug management, medical mistrust due to transphobia, HIV-related stigma and intersection with transphobia, life instability and drug use were barriers to PrEP acceptance
Storholm et al.[49] United States	MSM, reporting missed PrEP doses and recent illicit drug or alcohol use (n=30)	Qualitative Grounded Theory	Semi-structured interview and audio recording.	Risk perception, sexual well-being, increased openness in relationships with HIV-positive partners, memorization techniques for PrEP use, were aspects that favored PrEP use	Were not identified	Were not identified	Were not identified	Were not identified	Drug use (methamphetamine) and alcohol were the aspects that hinder the use of PrEP
Vaccher et al.[50] Australia	Gay and bisexual men, on PrEP therapy, HIV-positive or negative whose sexual partners were taking PrEP and Health professionals in the area (n=24)	Qualitative Descriptive	Sociodemographic and clinical questionnaire and semi-structured interview	Routine establishment of PrEP therapy, identification of difficulties, plans to manage contingency situations, drug reminder tools, support, recommendations and risk practices were facilitators for PrEP adherence	Were not identified	Were not identified	Were not identified	Were not identified	Were not identified

Watson et al.[51] United States	Transgender people and non-binary gender (n=37)	Qualitative Descriptive	Focus group, semi-structured interview, text messaging	Greater availability for PrEP, previous experience in taking daily medication, and motivation to lead an active and healthy life without fear of contracting HIV were facilitators for PrEP utilization	Were not identified	Were not identified	Were not identified	Were not identified	Access, discrimination by the health professional, side effects, interaction of hormone therapy with PrEP, poor STD protection, and hormone therapy with PrEP, poor protection against STDs, were barriers to PrEP use

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Table 4. Evaluation of the methodological quality of the included studies

Quantitative descriptive	Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low?	Is the statistical analysis appropriate to answer the research question?
Ferrer et al. [33]	Yes	Yes	Yes	No	Yes
Kwan et al. [37]	Yes	Yes	Yes	Yes	Yes
Lim et al. [38]	Yes	Yes	Yes	Yes	Yes
Salinas-Rodríguez et al. [40]	Yes	No	Yes	No	No
Sun et al. [41]	Yes	Yes	Yes	Yes	Yes
Whiteley et al. [42]	No	Yes	Yes	No	No
Quantitative randomized controlled trials	Is randomization appropriately performed?	Are the groups comparable at baseline?	Are there complete outcome data?	Are outcome assessors blinded to the intervention provided?	Did the participants adhere to the assigned intervention?
Closson et al. [32]	Yes	Yes	Yes	Yes	Yes
Martin et al. [39]	Yes	No	No	No	No
Quantitative nonrandomized	Are the participants representative of the target population?	Are measurements appropriate regarding both the outcome and intervention (or exposure)?	Are there complete outcome data?	Are the confounders accounted for in the design and analyses?	During the study period, is the intervention administered (or exposure occurred) as intended?
Fuchs et al. [34]	No	No	No	No	No
Hojilla et al. [35]	No	No	No	No	No
Hu et al. [43]	Yes	Yes	No	No	No
Koss et al. [36]	Yes	No	No	No	No
Qualitative	Is the qualitative approach appropriate to answer the research question?	Are the qualitative data collection methods adequate to address the research question?	Are the findings adequately derived from the data?	Is the interpretation of results sufficiently substantiated by data?	Is there coherence between qualitative data sources, collection, analyses and interpretation?
Alt et al. [52]	Yes	Yes	Yes	Yes	Yes
Cahill et al. [54]	Yes	Yes	Yes	Yes	Yes
Chemnasari et al.[53]	No	Yes	Yes	No	No
Franks et al. [55]	Yes	Yes	Yes	Yes	Yes
Liu et al. [44]	No	No	No	No	No
Longino et al. [45]	Yes	Yes	No	Yes	Yes
Ngure et al. [46]	No	No	No	No	No
Owens et al. [47]	No	No	No	No	No
Sevelius et al. [48]	Yes	Yes	Yes	Yes	Yes
Storholm et al. [49]	Yes	Yes	Yes	Yes	Yes
Vaccher et al. [50]	No	No	No	No	No
Watson et al. [51]	Yes	Yes	Yes	Yes	Yes
Mixed methods	Is there an adequate rationale for using a mixed methods design to address the research question?	Are the different components of the study effectively integrated to answer the research question?	Are the outputs of the integration of qualitative and quantitative components adequately interpreted?	Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?
Muwonge et al. [57]	Yes	No	No	No	No
Ssuna et al. [56]	No	No	No	No	No

Characteristics of included studies

According to type of study, 53,8 % corresponded to quantitative studies,[32,33,34,35,36,37,38,39,40,41,42,43] 38,4 % to qualitative studies[44,45,46,47,48,49,50,51,52,53,54,55] and 7,7 % to mixed studies.[56,57]

Fifty percent corresponded to studies conducted in the United States[32,34,36,38,41,46,47,48,50,51,54,55], the remaining 50 % to countries such as Spain (4,2 %),[33] Thailand (4,2 %),[53] Malaysia (4,2 %),[38] China (8,2 %),[41,43,44] Australia (4,2 %),[50] Mexico (4,2 %),[40] Peru (4,2 %) [45] and Kenya and Uganda (8,2 %),[36,57] Kenya (4,2 %),[46] Uganda

(4,2 %).[56] Studies included more than one key population [32,36,39,40,42,45,46,48-50,52,54,55,56,57] and one key population. [33,34,35,37,38,41,43,44,51,53] According to the methodological evaluation of the studies, 11 of them presented more than 80 % of the MMAT criteria.[31,32,33,38,39,42,45,45,48,49,51,52]

Aspects influencing adherence and compliance to oral PrEP were categorized according to 1) motivations to use PrEP, 2) barriers to PrEP use, 3) facilitators to PrEP use, 4) sexual decision making in the context of PrEP, 5) prospective content of PrEP education, and 6) perceived effective characteristics of personnel administering PrEP.[15]

Motivations for using PrEP

PrEP effectiveness,[34,42,43,44,46,49,50] sexual well-being,[38,46,49] and perceived high risk of HIV infection [36,38,41,44,45,48,49,50,56] were identified motivations for improved adherence and compliance.

Barriers to PrEP Use

Low access,[45,50,53] low socioeconomic status,[41,45,54] low schooling,[32,36] young adult and/or adolescent age group [36] and PrEP drug dosage were considered as barriers to PrEP use.[48,50,52,53,56] Likewise, negative feelings towards PrEP,[32,41,44,45,48,56] stigma[48,50,52,53,55] were presented as barriers. Additionally, side effects of PrEP,[32,44,48,51,54,56] low risk perception[44,53] were identified as barriers. Also, four studies evidenced dissatisfaction with medical care,[48,51,52,54] perception of low protection of oral PrEP against Sexually Transmitted Infections (STIs) as barriers to oral PrEP use.[35,51]

Facilitators for PrEP use

Three studies distinguished migration/ethnicity,[36,38,41] marital status [36,43] as facilitators. Also, willingness to use PrEP,[33,44,45,47,51,53] perceived ease of PrEP,[33,50,53] economic incentive,[37] and knowledge about PrEP [33,38,51,52] were facilitators for its use.

Sexual decision making in the PrEP context

Drug and/or alcohol use [36,48,49] and partner type (serodiscordant, plus 2 anal sex partners, and stable partners), [36,38,42] were decisions participants made when using PrEP.

Prospective Oral PrEP Education content

No PrEP educational content delivered by health care personnel was identified.

Perceived effective characteristics of staff administering oral PrEP.

Six studies identified health care team support,[34,35,47,50,57] PrEP drug cost coverage,[14] and intervention follow-up by hair testing in PrEP users [40] were characteristics perceived as effective by health care personnel providing care to key populations.

DISCUSSION

Motivations for PrEP use highlighted PrEP effectiveness and perceived high risk of HIV infection. The effectiveness of oral PrEP was shown to be one of the motivations influencing adherence and compliance. [34,42,43,44,46,49,50]. Similar results were identified in the literature, as one study found effectiveness to be a predictor for oral PrEP adoption ORa:2,48; (95 % CI: 1,89-3,25), p<0,001.[34] In addition, another study showed that once-daily consumption of Truvada® can reduce the risk of HIV infection by more than 90 % [5,58] and its implementation as a public health strategy is cost-effective.[7,8,9]

In addition, the perception of high HIV risk [36,37,38,41,44,45,48,50,56], was another motivation that influences the use of PrEP. Similar results were identified in the literature, a study in France identified that patients with higher perceived risk of contracting HIV have higher adherence to oral PrEP (p < 0,001) [59] and another in the United States, corroborated that risk perception is a predictor for PrEP adoption ORa:1,04; (CI: 1,02-1,07), p < 0,01.[34]

In relation to barriers to PrEP use, negative feelings about PrEP, stigma and side effects of PrEP stood out. Negative feelings about PrEP were shown to be a barrier to PrEP use [32,41,44,45,56]. Likewise, a study in the United States corroborated those negative feelings about PrEP is a barrier to discontinuation of PrEP.[60]

Stigma was identified as a second barrier to PrEP use.[48,50,52,53,55] These findings were corroborated by a study which showed that high levels of stigma were associated with low adherence to treatment ORa = 2,74, (95 % CI: 1,13-6,61) p<0,01.[61]

Side effects were identified as a third barrier to PrEP use.[32,44,48,51,54,56] These findings were like a study in Germany, which showed an association between side effects and low adherence to the drug (p=0,015).[62] Likewise, another study in the United States showed that the presence of side effects to the use of the drug is a barrier that leads to discontinuation of PrEP.[60]

According to the facilitators for the use of PrEP, willingness was identified.[33,44,45,47,51,53] These findings were

corroborated by a study in China, which found that willingness was associated with intention and adherence to PrEP and in turn with high level of schooling (postgraduate) ORa = 1,90, (95 % CI:1,11-3,26); p<0,001.[61] Controversial outcomes were identified as socioeconomic factors, migration/ethnicity,[39,40,55] marital status,[36,63] these findings were corroborated by one study.[43]

According to sexual decision making in the context of PrEP, the use of drugs and/or alcohol stood out.[36,48,49] Similar results were found in a study in the United States, which showed that patients who consume any licit substance are more likely to adopt PrEP among the key population ORa: 2,27, (95 % CI: 0,92-5,56), p < 0,001.[34]

According to prospective content of oral PrEP education, they were not identified as being delivered by health personnel. According to the characteristics perceived as effective of the personnel who administered oral PrEP, the support of the health team stood out.[34,35,47,48,50,57] Similar results were identified.[64,65]

The drug dose was considered a barrier,[48,50,52,53,56] although some studies have corroborated this finding and show that it improves adherence and compliance to PrEP in other pharmacological presentations such as cervicovaginal [66] and injectable [67], there is other evidence that it has not been shown to be detrimental to adherence and compliance to PrEP.

The present review showed the aspects that influence adherence and compliance to PrEP in key populations. It is necessary to stimulate combination prevention, through interventions that detect and address these aspects for the improvement of adherence and compliance in the most vulnerable population.

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