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Overview of systematic reviews on the risks and benefits of HIV pre-exposure prophylaxis available in the Brazilian Unified Health System

Overview de revisões sistemáticas sobre riscos e benefícios da profilaxia pré-exposição ao HIV disponível no Sistema Único de Saúde do Brasil

Overview de las revisiones sistemáticas sobre los riesgos y beneficios de la profilaxis previa a la exposición (PrEP) al VIH disponible en el sistema público de salud de Brasil

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Abstract

This is an overview of systematic reviews aimed at assessing the risks and benefits of HIV PrEP available through SUS. The clinical outcomes of interest were reduction in HIV incidence, sexual behavior and risk compensation, ARV medications, incidence of other STIs, and ARV resistance in cases of seroconversion. For this purpose, a search was conducted in the databases Medline via PubMed, Virtual Health Library (VHL), Epistemonikos, and Cochrane Library up to January 2022, without language restrictions. The reviews were required to include PrEP available through the SUS (TDF/FTC), with placebo as the comparator. Four systematic reviews published between 2016 and 2021 were included. All reviews analyzed different adverse effects of PrEP, identifying a positive association with changes in renal function, reduced BMD, gastrointestinal alterations (nausea and vomiting), and >5% body weight loss. The efficacy of PrEP was confirmed in cases of moderate and high adherence. No increase in STI rates, risk compensation, or ARV resistance in cases of seroconversion was identified. Therefore, TDF/FTC-based PrEP available through the Brazilian SUS is effective in reducing HIV incidence among individuals at higher risk who maintain moderate to high adherence. However, it is an additive prevention measure offered to asymptomatic individuals. In this context, shared decision-making regarding its indication is important, as not everyone will benefit equally and there is a risk of adverse events.

Keywords: Pre-exposure prophylaxis; Emtricitabine, tenofovir disoproxil fumarate drug combination; Disease prevention.

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Resumo

Trata-se de um *overview* de revisões sistemáticas com o intuito de avaliar riscos e benefícios da Profilaxia Pré-Exposição (PrEP) ao Vírus da Imunodeficiência Humana (HIV) disponível no Sistema Único de Saúde (SUS) do Brasil. Os desfechos clínicos de interesse foram redução da incidência de HIV, comportamento sexual e risco de compensação, efeitos adversos dos medicamentos antirretrovirais (ARV), incidência de outras Infecções Sexualmente Transmissíveis (ISTs) e resistência a ARV em caso de soroconversão. Para isso, realizou-se uma busca nas bases de dados *Medical Literature Analysis and Retrieval System Online* (*Medline*) via Pubmed, Biblioteca Virtual em Saúde (BVS), *Epistemonikos* e *Cochrane Library* até janeiro de 2022, sem restrição de idiomas. As revisões deveriam contemplar a PrEP disponível no SUS (fumarato de tenofovir desoproxila/entricitabina – TDF/FTC), tendo como comparador o placebo. Foram incluídas quatro revisões sistemáticas publicadas entre 2016 e 2021. A totalidade das revisões analisou diferentes efeitos adversos da PrEP, identificando associação positiva com alteração da função renal, redução da Densidade Mineral Óssea (DMO), alteração gastrointestinal (náusea, vômitos) e perda ponderal >5% do peso corporal. Foi confirmada a eficácia da PrEP nos casos de moderada e alta adesão. Não foram identificados aumento no índice de ISTs, risco de compensação e resistência aos ARV nos casos de soroconversão. Portanto, a PrEP com TDF/FTC disponível no SUS do Brasil é eficaz na redução da incidência de HIV em pessoas de maior risco que mantêm moderada a alta aderência. No entanto, é uma medida de prevenção aditiva, ofertada a pessoas assintomáticas. Nesse sentido, é importante compartilhar a decisão sobre sua indicação, uma vez que nem todos se beneficiarão de igual maneira e há risco de eventos adversos.

Palavras-chave: Profilaxia pré-exposição; Combinação emtricitabina e fumarato de tenofovir desoproxila; Prevenção de doenças.

Resumen

Realizó un resumen de las revisiones sistemáticas para evaluar los riesgos y beneficios de la PrEP disponibles en el SUS en Brasil. Los resultados clínicos de interés fueron la reducción de la incidencia del VIH, el comportamiento sexual y el riesgo de compensación, los efectos adversos de los ARV, la incidencia de otras ETS y la resistencia a los ARV en caso de seroconversión. Realizó una búsqueda en las bases de datos Medline vía Pubmed, Biblioteca Virtual en Salud (BVS), Epistemonikos y Cochrane Library hasta enero de 2022, sin restricción de idioma. Las revisiones deben contemplar la PrEP disponible en el SUS (TDF/FTC), con placebo como comparador. Se incluyeron 4 revisiones sistemáticas publicadas entre 2016 y 2021. Todas las revisiones analizaron diferentes efectos adversos de la PrEP identificando una asociación positiva con cambios en la función renal, reducción de la DMO, cambios gastrointestinales (náuseas, vómitos) y pérdida de peso corporal >5%. La efectividad de la PrEP se confirmó en casos de adherencia moderada y alta. No se identificó aumento en la tasa de ETS, riesgo de compensación y resistencia a los ARV en los casos de conversión sérica. En conclusión, la PrEP con TDF/FTC disponible en el SUS de Brasil es eficaz para reducir la incidencia de VIH en personas con mayor riesgo que mantienen una adherencia moderada a alta. Sin embargo, es una medida de prevención aditiva, ofrecida a personas asintomáticas. En este sentido, es importante compartir la decisión sobre su indicación, ya que no todos se beneficiarán por igual y existe riesgo de eventos adversos.

Palabras clave: Profilaxis pre-exposición; Combinación emtricitabina y fumarato de tenofovir disoproxil; Prevención de enfermedades.

INTRODUCTION

Pre-exposure prophylaxis (PrEP) for Human Immunodeficiency Virus (HIV) is an effective intervention for preventing HIV infection [1]. It involves the use of antiretroviral (ARV) medications by HIV-negative individuals at increased risk of acquiring the virus, and its effectiveness depends on adherence.[1]

The PrEP regimen provided by Brazil's Unified Health System (*Sistema Único de Saúde* – SUS) consists of a loading dose of two tablets of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) on the first day of use, followed by one tablet daily. Following the September 2022 update to the Clinical Protocol and Therapeutic Guidelines (CPTGs), eligibility for PrEP was expanded to include all sexually active adults and adolescents aged 15 years old and older who are at increased risk of HIV infection[1]. The previous protocol restricted PrEP use to key populations with an estimated HIV incidence exceeding 5%, substantially higher than the estimated HIV prevalence of 0.4% in the general Brazilian population[2]. These populations include men who have sex with men (MSM), members of the LGBTQIA+ community, sex workers, HIV-serodiscordant couples engaging in condomless sex, and individuals with recurrent sexually transmitted infections (STIs) and/or repeated use of HIV post-exposure prophylaxis (PEP). This policy is part of the Ministry of Health's Combined Prevention strategy, which integrates biomedical, behavioral, and structural

interventions to reduce the risk of HIV infection. Similarly, since 2019, the US Preventive Services Task Force (USPSTF) has recommended PrEP for adults and adolescents at increased risk of HIV acquisition, assigning it a Grade A recommendation.[3]

PrEP exemplifies "additive prevention," a concept defined by Rose,[4,5] which refers to the prescription of an artificial product to prevent a potential future pathological event. It also represents a high-risk strategy in which individuals belonging to a risk group (in this case, sexually active adults and adolescents at increased risk of HIV infection) are identified and invited to participate in preventive interventions, namely PrEP. Although this approach targets those at greatest risk, thereby facilitating more efficient allocation of resources and greater public acceptance of the proposed interventions, it "tends to medicalize people by turning asymptomatic individuals into patients,"[4] who subsequently begin taking medication, attending clinical consultations, and undergoing periodic testing as frequently as individuals diagnosed with HIV. Moreover, prescribing medication to address risk factors may create a vicious cycle, as "anyone taking medication is, by definition, a patient."[6,7]

Therefore, given the importance of shared decision-making regarding treatment, with consideration of each individual's sexual practices and corresponding protection needs, this study aimed to evaluate the risks and benefits of PrEP provided through the SUS.

METHODS

This overview of systematic reviews was conducted in accordance with the methodological guidelines for the development of technical-scientific reports issued by the Ministry of Health[8] and the PRIOR Checklist[9].

The literature search was conducted in the Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, the Virtual Health Library (VHL), Epistemonikos, and the Cochrane Library. Systematic reviews and meta-analyses published in these databases from inception through January 2022 were included, with no language restrictions. The research question was formulated using the PICO framework: population (P) = sexually active HIV-negative individuals at increased risk of acquiring HIV; intervention (I) = PrEP provided through SUS (tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) 300/200 mg daily); comparator (C) = placebo or no treatment; and outcomes (O) = reduction in HIV incidence, sexual behavior and risk compensation, adverse drug effects, incidence of other STIs, and ARV resistance among individuals who experienced seroconversion.

The search strategy used in PubMed was as follows: ((Pre-Exposure Prophylaxis [MeSH]) OR (Pre Exposure Prophylaxis) OR (Pre-Exposure Prophylaxi) OR PrEP OR (Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination [MeSH]) OR Truvada) AND (HIV Infections [MeSH] OR HIV [MeSH] OR HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immunodeficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus))) AND (systematic review [pt] OR Systematic Reviews as Topic [MeSH] OR systematic review [tiab]). The search strategies used for the other databases are provided in the Supplementary Material.

Search results were imported into Rayyan, where duplicates were removed and articles were screened by title and abstract. Any uncertainties regarding study selection were resolved through discussion among the authors. The full texts of the selected articles were subsequently assessed for eligibility, with any disagreements resolved by consensus among the authors. Finally, the included systematic reviews and meta-analyses were evaluated according to the primary studies they contained.

Older reviews were excluded when all of their primary studies had been fully incorporated into more recent and comprehensive reviews. Data were extracted using Microsoft Excel and included the following information: authors, year of publication, objective of the systematic review, study population, participant characteristics (number, gender, and sexual and behavioral practices), interventions evaluated, outcomes, and results.

The methodological quality of the included studies was assessed using the AMSTAR 2 tool for the critical appraisal of systematic reviews, and the results are summarized in Chart 1.

Chart 1. Characteristics of the systematic reviews.

Author, year	Population characteristics	Outcomes analyzed	AMSTAR 2
Shahini Shah, 2021[10]	Not specified	Adverse events: >5% weight loss, gastrointestinal adverse events (vomiting, diarrhea, nausea, grade 2 or higher adverse events)	Critically low
Benjamin Baranek, 2020[11]	Not specified	Adverse events: impact on bone health over 48 weeks (reduced BMD and fractures)	Low
Roger Chou, MD, 2019[12]	Heterosexual men and women, MSM, people who inject drugs	Efficacy, adverse events (renal and gastrointestinal), incidence of STIs, mortality, treatment discontinuation due to serious adverse events	Low
Virginia Fonner, 2016[13]	People who inject drugs, serodiscordant couples, MSM, transgender women, heterosexual women and men	Efficacy, adverse events (overall and grade 3 or 4), risk behavior, antiretroviral resistance	Low

BMD: Bone Mineral Density; MSM: Men Who Have Sex with Men; STIs: Sexually Transmitted Infections.

RESULTS

A total of 795 studies were initially identified, of which 215 were excluded as duplicates. The remaining articles were screened by title and abstract, followed by full-text assessment, resulting in the inclusion of 17 reviews. The primary studies included in each review, along with their respective objectives, were then analyzed individually using Microsoft Excel. Based on this analysis, 13 reviews were excluded, yielding a final sample of four reviews, as illustrated in the flowchart presented in Figure 1. Study selection was conducted exclusively by the authors, without the involvement of third parties.

Four systematic reviews with meta-analyses, published between 2016 and 2021, were included in this overview. The study populations comprised cisgender men and women, MSM, people who inject drugs, transgender women, and serodiscordant couples, all aged 18 years or older. All four reviews evaluated adverse effects associated with PrEP[10-13] compared with placebo. Two reviews[12,13] also assessed PrEP efficacy, sexual behavior, and the incidence of STIs, whereas only one review examined ARV resistance among individuals who experienced seroconversion.[13] The main characteristics of the included reviews are summarized in Table 1.

The methodological quality assessment using AMSTAR 2 indicated that only one review received an overall rating of critically low. This review exhibited major flaws in critical domains, including the absence of a predefined research protocol, an inadequately described search strategy, and the lack of appropriate methods for assessing risk of bias, all of which are likely to directly affect the interpretation

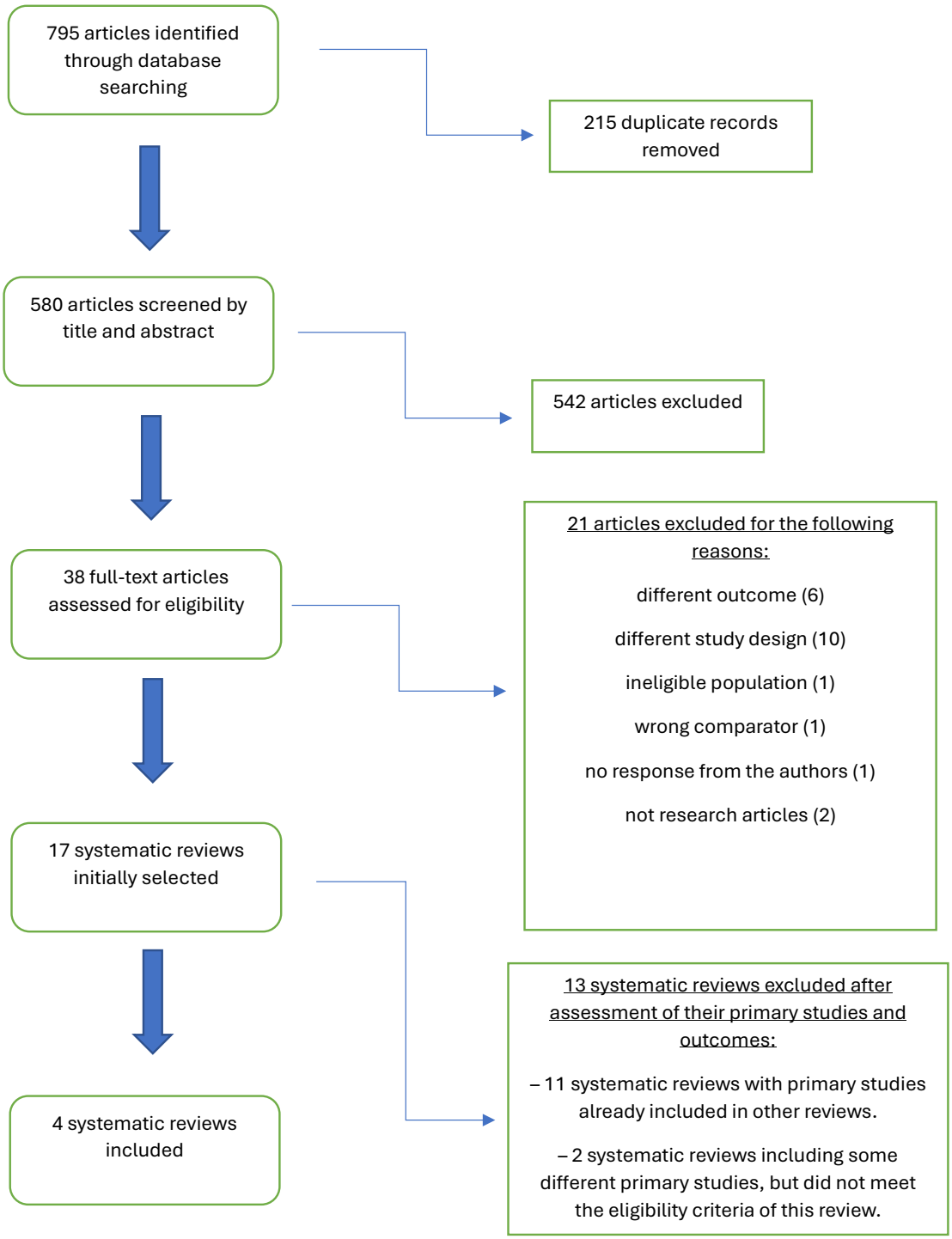

Figure 1. Flowchart of the study selection process.

and generalizability of its findings regarding the impact of weight loss in PrEP users receiving TDF. The remaining reviews received an overall rating of low, each with only one flaw in a critical domain, suggesting greater confidence in their findings. Among these, the review by Chou et al.[12] achieved the highest overall methodological quality, with points deducted solely because study selection was restricted to publications in English. The complete quality assessment of each review is provided in the Supplementary Material.

Table 1. Main statistically significant outcomes reported in the included systematic reviews.

Author, year	Total population	No. of PrEP events/ population × No. of placebo events/population	No. of RCTs	Outcome analyzed	Result	NNT/ NNH
Shahini Shah, 2021[10]	16,135	270/9,444 × 249/6,691	6	>5% weight loss	OR 1.48; 95%CI 1.06–2.07; p=0.005	250
Shahini Shah, 2021[10]	9,109	253/5,049 × 139/4,060	5	Vomiting (grades 1–4)	OR 1.81; 95%CI 1.20–2.73; p<0.005	62
Benjamin Baranek, 2020[11]	1,350	NR	4	Reduced lumbar spine BMD	-0.82; 95%CI -1.28; -0.37; p=0.0004	NE
Benjamin Baranek, 2020[11]	1,350	NR	4	Reduced total spine BMD	-0.81; 95%CI -1.22; -0.4; p=0.0001	NE
Roger Chou, MD, 2019[12]	10,626	158/5,962 × 224/4,664	8	Efficacy	RR 0.44 [95%CI 0.27–0.72] p<0.001	33
Roger Chou, MD, 2019[12]	10,738	174/6,037 × 89/4,701	9	Renal adverse events	RR 1.54 (1.21–1.96) p=0.0005	125
Roger Chou, MD, 2019[12]	10,740	246/6,038 × 105/4,702	9	Gastrointestinal adverse effects (primarily nausea)	RR 1.84 (1.26–2.70) p=0.002	54
Virginia Fonner, 2016[13]	11,381	NR	7	Truvada PrEP efficacy	RR 0.51 (0.31–0.83) p=0.007	NE

PrEP: Pre-Exposure Prophylaxis; RCTs: Randomized Controlled Trials; NNT/NNH: Number Needed to Treat/Number Needed to Harm; OR: odds ratio; 95%CI: 95% confidence interval; NR: not reported; BMD: Bone Mineral Density; NE: not estimated; RR: relative risk.

HIV incidence among PrEP users

The review by Chou et al.,[12] which informed the update of the USPSTF clinical recommendations, [2] confirmed the efficacy of TDF/FTC as PrEP in reducing the risk of HIV infection (RR 0.44 [95%CI 0.27–0.72; I^2=67%]; p<0.001). PrEP was also effective across subgroup analyses based on HIV risk categories (MSM and transgender women, heterosexual men and women, and people who inject drugs). USPSTF further evaluated the association between PrEP adherence and its efficacy in reducing the risk of HIV acquisition. Higher adherence (≥70% of prescribed doses taken) was associated with a greater reduction in HIV acquisition risk and a substantial decrease in study heterogeneity (RR 0.27 [95%CI 0.19–0.39; I^2=0%]; p<0.001). When adherence ranged from 40 to 70% of prescribed doses, a significant reduction in HIV acquisition risk was still observed (RR 0.51 [95%CI 0.38–0.70]; p<0.001). However, when adherence fell below 40%, no statistically significant difference was observed compared with placebo.

The review by Virginia A. Fonner[13] also confirmed the efficacy of the TDF/FTC combination as PrEP. A meta-analysis of 7 studies (n=11,381) demonstrated a 49% reduction in the risk of HIV acquisition (RR 0.51 [95%CI 0.31–0.83]; p=0.007). Stratification by adherence substantially reduced overall heterogeneity, and PrEP demonstrated greater efficacy in studies with high and moderate levels of adherence. However, the analysis did not distinguish between users receiving TDF/FTC and those receiving TDF alone as PrEP, which may limit the interpretation of these findings.

Sexual behavior, risk compensation, and incidence of other STIs

In the review by Chou et al.,[12] no increased risk of incident STIs was observed among PrEP users. The infections evaluated included syphilis, gonorrhea, chlamydia, and herpes simplex virus infection. All but one of the included studies were blinded, which may have influenced the interpretation of the findings. Although the review by Fonner[13] did not perform a meta-analysis because of differences across studies in the assessment of condom use and number of sexual partners, it found no differences between PrEP and placebo users for either outcome.

Adverse effects of the medications that make up PrEP

The review by Shah et al.[10] evaluated the association between TDF-based PrEP and clinically significant weight loss, defined as a reduction of ≥5% in body weight. The included primary studies assessed both TDF monotherapy and the TDF/FTC combination, demonstrating a 48% increase in the odds of experiencing weight loss of ≥5% compared with placebo (OR 1.48 [95%CI 1.06–2.07]; p=0.005) in a pooled population of 16,135 participants from 6 studies.

The review also evaluated gastrointestinal adverse events of any severity, as well as those of grade 2 or higher, because of their potential contribution to weight loss. Compared with placebo, PrEP use was associated with an increased risk of vomiting (OR 1.81 [95%CI 1.20–2.73]; p<0.005). No significant differences were observed for the other adverse events evaluated (nausea, decreased appetite, and diarrhea), including grade 2 or higher events.

In the review by Benjamin Baranek et al.,[11] the analysis focused on the effects of TDF alone or the TDF/FTC combination on bone mineral density (BMD) compared with placebo over 48 weeks of follow-up. Across the four studies analyzed, PrEP users experienced a significant decline in BMD at both the lumbar spine (-0.82 [95%CI -1.28; -0.37], p=0.0004) and the total hip (-0.81 [95%CI -1.22; -0.4], p=0.0001). However, no significant difference was observed in fracture incidence between the PrEP and placebo groups.

In the review by Chou et al.,[12] analyses that evaluated users of TDF/FTC separately from those receiving TDF alone as PrEP identified an increased risk of gastrointestinal adverse events, primarily nausea (RR 1.84 [95%CI 1.26–2.70], p=0.002). An increased risk of changes in renal function was also observed (RR 1.54 [95%CI 1.21–1.96], p=0.0005). Renal dysfunction was defined as an increase of at least 1 grade in serum creatinine levels; however, these changes were reversible following PrEP discontinuation. Compared with placebo, no increased risk of serious adverse events, discontinuation of PrEP due to adverse drug reactions, or mortality was identified. Likewise, no increased risk of fractures was observed across the six included studies, including the 2012 Partners PrEP Study Team, which had a maximum follow-up period of 36 months.

The review by Fonner[13] found no significant differences between the PrEP and placebo groups in the proportion of participants experiencing any adverse events (OR 1.02 [95%CI 1.00–1.04] p=0.06) or grade 3 or 4 adverse events (OR 1.07 [95%CI 0.94–1.21] p=0.32).

Antiretroviral resistance in cases of seroconversion

The review by Fonner[13] was the only one to evaluate ARV resistance associated with PrEP among individuals who experienced seroconversion, assessing resistance at two time points: study baseline (pre-

randomization) and post-randomization. Among the 533 participants who acquired HIV after randomization, 6 cases of drug-resistant infection were identified — five emtricitabine-associated resistance mutations in the PrEP group and one mutation in the placebo group. However, this difference was not statistically significant. No TDF-associated resistance mutations were identified in any of the cases.

DISCUSSION

PrEP has been shown to be an effective preventive intervention for reducing HIV incidence, with a Number Needed to Treat (NNT) of 33.[12] Its effectiveness increases with higher adherence to the daily TDF/FTC regimen.[12,13] PrEP has also been well tolerated by most users, although the most commonly reported adverse effects include changes in renal function and gastrointestinal symptoms. The calculated Number Needed to Harm (NNH) was 125 for renal impairment[12] and 54 for gastrointestinal adverse effects, primarily nausea.[12] In another review, the NNH for gastrointestinal adverse effects, specifically vomiting, was 62.[10] Although these adverse events are relatively uncommon, it is important to recognize that PrEP is a preventive intervention rather than a therapeutic one. Its purpose is not to treat an existing condition but to prevent a potential future health event. Therefore, the anticipated benefits should clearly outweigh the potential risks, and this information should be communicated to patients as part of the decision-making process.

An impact on weight loss (>5% of body weight) and reductions in bone mineral density BMD was also identified among PrEP users receiving TDF; these changes may be associated with an increased risk of fractures, particularly considering the long-term use of PrEP.[14] Although studies have not identified an increased risk of fractures,[12,13] their mean follow-up periods were insufficient to adequately assess this outcome. Of particular concern are adolescents; despite representing a population with increasing HIV incidence and high-risk sexual practices,[1] they may experience a greater impact on bone health because they are in a critical period for achieving peak bone mass, which could result in significant long-term consequences.[15]

In the reviews analyzed in this study, adolescents were an exclusion criterion for the primary studies, and all participants were older than 18 years. Since 2012, the US Food and Drug Administration (FDA) has approved the use of TDF/FTC as PrEP in the United States for adolescents weighing ≥35 kg, and subsequent studies have been conducted to specifically evaluate this population. The demonstration study by Sybil G. Hosek[15] was the first to assess the safety and efficacy of TDF/FTC in a cohort of adolescent MSM aged 15 to 17 years. Despite the small sample size (n=78) and substantial loss to follow-up, which may limit the generalizability of the findings, the study supported the recommendation of PrEP use for this age group. However, it identified a mild but statistically significant decline in total-body BMD Z-score over a follow-up period of up to 48 weeks, suggesting that bone accrual among PrEP users in this age group may have been lower than expected. This finding was also supported by a follow-up study conducted by Peter L. Havens[16] after PrEP discontinuation, which demonstrated that lumbar spine and whole-body BMD remained below expected baseline levels for 48 weeks after discontinuation among participants aged 15 to 19 years. These findings raise an important concern that should be discussed with users, particularly adolescents, when considering PrEP initiation, along with the assessment of additional risk factors that may further affect bone health, such as smoking, oral corticosteroid use, and family history of fractures, among others.[14]

Regarding the incidence of other STIs or changes in sexual behavior, also referred to as risk compensation, no positive association was identified among PrEP users.[12,13] Assessment parameters

included rapid and/or serological tests performed during periodic follow-up visits, as well as participant-reported condom use during sexual activity and number of sexual partners. However, most primary studies were randomized controlled trials (RCTs), in which blinding may influence individual behavior and risk perception, as participants are unaware of whether they are actually receiving PrEP as a preventive intervention or placebo.

When the studies included in the reviews that compared PrEP with no PrEP (no treatment) were analyzed separately,[12,13] which may more accurately reflect real-world scenarios, no statistically significant differences were identified regarding behavioral changes or the incidence of other STIs. However, a meta-analysis by Michael W. Traeger,[17] the first review to evaluate risk compensation among MSM using PrEP, which included eight observational studies and uncontrolled open-label trials (n=4,388), identified an increase in STIs, particularly anorectal STIs, suggesting an increase in condomless receptive anal sex after PrEP initiation.[13] Another 13 studies (n=5,008) included in the same review identified changes in condom use, with most reporting an increase in unprotected sex. These discrepancies among reviews highlight the need for further studies using models that more closely reflect real-world conditions and allow assessment of PrEP's actual impact on users' perceptions of safety and their level of concern regarding other STIs, while maintaining frequent STI screening and reinforcing guidance on safer sexual practices.

The analysis of ARV resistance did not identify a significant association between PrEP use and the development of resistance among individuals who experienced seroconversion during PrEP use.[13] Most resistance cases reported in the included studies occurred in participants who were already infected with HIV at the time of trial enrollment but whose infection had not been detected before randomization. This finding underscores the importance of HIV testing and the exclusion of individuals with acute or chronic HIV infection before PrEP initiation. Furthermore, attributing the identified resistance cases exclusively to PrEP is limited, as individuals may acquire an HIV strain that already harbors resistance-associated mutations.

This overview has several limitations. By including only systematic reviews — the most recent of which was published in 2021 — it may not have captured more recent evidence on PrEP, a rapidly evolving field with numerous ongoing studies and frequent updates. In addition, the analysis was restricted to the PrEP regimen currently available through the SUS, excluding other PrEP options available internationally, including some that are currently under investigation for future implementation in Brazil. Furthermore, evidence remains limited for certain population groups that were not represented in the primary studies included in the analyzed reviews, such as sex workers and pregnant women. Additional studies are needed to establish the effectiveness of PrEP in these populations before its risks and benefits can be adequately assessed. Although the search strategy was intentionally limited to freely accessible databases, the exclusion of Embase may also be considered a limitation. Finally, the overall low methodological quality of the reviews included, as assessed by AMSTAR, should be considered when interpreting the findings.

The analysis and discussion of PrEP represent a timely and highly relevant topic, particularly when considering aspects beyond the efficacy consistently demonstrated under conditions of high adherence. Objectively identifying the main adverse effects, the potential for changes in sexual behavior, and the risk of drug resistance, together with estimates of the NNT and NNH, enables patients to make more informed decisions regarding the risks and benefits of initiating PrEP.

The discussion and critical appraisal of preventive interventions have become increasingly prominent because of the considerable potential for both benefit and harm associated with medical and public health interventions applied to otherwise healthy individuals, for whom the use of medications, periodic testing, or

regular medical consultations would not otherwise be indicated. This tendency for preventive interventions to promote medicalization increases the institutional, social, and psychological costs associated with the proposed measures. By treating risk factors as though they were diseases, such interventions transfer the values and attitudes traditionally associated with illness to the domain of prevention.[18]

When medications are prescribed to treat an established disease, treatment response can be assessed by evaluating clinical improvement or disease progression, thereby informing decisions regarding treatment continuation or modification. In contrast, when medications are prescribed to reduce the risk of developing a disease, the outcome is inherently probabilistic. If the disease is prevented or never develops, the preventive intervention may be continued indefinitely. Therefore, although PrEP is effective in reducing HIV incidence among individuals at high risk who maintain moderate to high levels of adherence, its use should also be considered within the framework of P4.

FINAL CONSIDERATIONS

PrEP with TDF/FTC, as provided through SUS, is effective in reducing HIV incidence among individuals at high risk who maintain moderate to high levels of adherence. However, it is an additive preventive intervention offered to asymptomatic individuals. Consequently, decisions regarding its prescription should be based on a shared decision-making process, recognizing that not all individuals will derive the same benefit and that there is a risk of adverse events, particularly among populations not directly evaluated in clinical trials, such as adolescents and certain at-risk groups for whom the available evidence has been extrapolated.

CONFLICT OF INTERESTS

Nothing to declare.

AUTHORS' CONTRIBUTIONS

GT: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. JCO: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing.

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APPENDIX

AMSTAR 2

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☑ Population
- ☑ Intervention
- ☑ Comparator group
- ☑ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

☑ Yes
☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

☐ Yes
☐ Partial Yes
☑ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☑ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

☑ Yes
☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☑ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☑ justified publication restrictions (eg, language)

For Yes, should also have (all the following):
- ☐ searched the reference lists/bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

☐ Yes
☐ Partial Yes
☑ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer

☑ Yes
☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers achieved consensus on which data to extract

☑ Yes

AMSTAR 2

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Search Strategy VHL

((mh:(Pre-Exposure Prophylaxis)) OR (mh:(Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination)) OR (Pre Exposure Prophylaxis) OR (Pre-Exposure Prophylaxi) OR PrEP OR Truvada) AND ((mh:(HIV infections)) OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR (human immunodeficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus)) OR (mh:(HIV))) AND ((mh:(Systematic Reviews as Topic)) OR (systematic review))

Epistemonikos

((Pre-Exposure Prophylaxis) OR (Pre Exposure Prophylaxis) OR (Pre-Exposure Prophylaxi) OR PrEP OR (Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination) OR Truvada) AND ((HIV infection*) OR HIV OR (human immunodeficiency virus) OR (human immuno deficiency virus) OR (human immune deficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus))

Filter: Systematic review

Cochrane

Date Run: 24/01/2022 22:31:28

Comment: ID Search Hits

#1 MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees 239

#2 MeSH descriptor: [Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination] explode all trees 201

#3 ((Pre Exposure Prophylaxis) OR (Pre-Exposure Prophylaxi) OR PrEP OR Truvada):ti,ab,kw 2385

#4 MeSH descriptor: [HIV Infections] explode all trees 13325

#5 MeSH descriptor: [HIV] explode all trees 3223

#6 (hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR (human immunodeficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus))):ti,ab,kw 25481

#7 (#1 OR #2 OR 3) AND (#4 OR #5 OR #6) 16731