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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is pre-exposure prophylaxis effective for preventing HIV infection in men who have sex with men?

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Abstract

INTRODUCTION
Increasing rates of HIV infection remain of concern, especially for high-risk groups such as men who have sex with men. Oral pre-exposure prophylaxis has emerged as an alternative to prevention. However, doubts persist in patients and physicians about its effectiveness.

METHODS
To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

RESULTS AND CONCLUSIONS
We identified six systematic reviews including twelve studies overall, of which six were randomized trials. We concluded the use of oral pre-exposure prophylaxis reduces the probability of HIV infection in men who have sex with men, has few or no adverse effects, and is a measure with a good balance between benefits, risks and costs.

Problem

Despite increased community awareness, HIV infection rates continue to rise. One of the high-risk group is men who have sex with men, so better prevention strategies are required. The use of antiretroviral drugs in uninfected individuals, or pre-exposure prophylaxis (PrEP), has emerged as a promising tool for prevention in individuals at high risk of HIV infection. The most commonly used combination of PrEP has been oral emtricitabine with tenofovir disoproxil fumarate, and to a lesser extent tenofovir disoproxil fumarate alone. Despite the approval of the first as PrEP by the FDA in 2012, physicians and patients still question the effectiveness and safety of this measure.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and

reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Pre-exposure prophylaxis reduces HIV infection in men who have sex with men, with minimal or no adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found six systematic reviews [1],[2],[3],[4],[5],[6] that included 12 primary studies reported in 23 references [7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29]. Six corresponded to randomized controlled trials reported in 17 references [7],[8],[11],[14],[15],[16],[18],[19],[20],[21],[23],[24],[25],[26],[27],[28],[29]. This table and the summary in general are based on the latter, given that observational studies did not increase the certainty of the existing evidence, nor did they provide relevant additional information.
What types of patients were included*	The patients included in the trials were HIV uninfected men who have sex with men, over 18 years of age, and considered at high risk of HIV infection (due to a history of high number of sexual partners, sexual intercourse without condom use, sex with people with sexually transmitted diseases, or sex in exchange for money).
What types of interventions were included*	All trials evaluated the use of oral PrEP in conjunction with standard prevention (including education and provision of condoms). Five evaluated the use of emtricitabine/tenofovir [11],[14],[20], [23],[29] and one the use of tenofovir alone [25]. Five trials evaluated against placebo [11],[14],[23],[25],[29] and three against a non-treatment group [14],[20],[25]. Five used PrEP on a daily basis [11],[14],[20],[25],[29] and one intermittently, before and after having sex [23]. One trial used behavioral therapy as a co-intervention [14] and one trial was pragmatic and open-label [20]. One trial included a small group of women [29], but since the vast majority of the participants were men who had sex with men, it was included in the analysis.
What types of outcomes were measured	The main outcomes analyzed were the rate of HIV infection and adverse effects. Qualitatively analyzed outcomes included changes in risk behaviors, mainly condom use objectified by interviews [14],[25] or indirectly by incidence of other sexually transmitted diseases [20]. The average follow-up of the trials was 15 months, with a range between 4 and 33 months.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

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Summary of Findings

The information on the effects of oral PrEP in men who have sex with men is based on six trials [11],[14],[20],[23],[25],[29] which included 3974 patients.
It was not possible to extract enough information from the reviews identified to reconstruct the meta-analysis of HIV incidence. Therefore, the information presented is based on the results of the meta-analysis of a systematic review [1] that is based on four trials [11],[23],[25],[29] that included 3371 patients.
The information on adverse events is based on three trials [11],[14],[25] whose data were reusable from systematic reviews and included 2957 patients. The information on changes in condom use is based on three trials [14],[20],[25] that compared against no treatment, whose data were described qualitatively in the systematic reviews and included 1003 patients.

The summary of findings is as follows:

- Pre-exposure prophylaxis reduces HIV infection in men who have sex with men. The certainty of the evidence is high.
- Pre-exposure prophylaxis reduces leads to minimal or no increase in adverse effects. The certainty of the evidence is high.
- Pre-exposure prophylaxis might result in little or no difference in terms of condom use in men who have sex with men. The certainty of the evidence is low.

Oral PrEP for prevention of HIV infection in men who have sex with men				
Patients	HIV uninfected men who have sex with men			
Intervention	Oral pre-exposure prophylaxis (PrEP)			
Comparison	Placebo or no treatment			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT Oral PrEP	WITH Oral PrEP		
	Difference: patients per 1000			
HIV incidence	50 per 1000	17 per 1000	RR 0.34 (0.15 to 0.80)	⊕⊕⊕⊕ High
	Difference: 33 less (Margin of error: 10 less to 42 more)			
Adverse effects	63 per 1000	72 per 1000	RR 1.14 (0.71 to 1.83)	⊕⊕⊕⊕ High
	Difference: 9 more (Margin of error: 18 less to 52 more)			
Condom use	No differences between treated and untreated patients		--	⊕⊕◯◯[1,2] Low

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT Oral PrEP** is based on the risk in the control group of the trials. The risk **WITH Oral PrEP** (and its margin of error) is calculated from relative effect (and its margin of error).

[1]One level of certainty of evidence was decreased due to the use of non-validated measurements as indirect evidence for the outcome.
[2]One level of certainty of evidence was decreased due to risk of bias in the included studies.

Follow the link to access the interactive version of this table (Interactive Summary of Findings - iSoF)

About the certainty of the evidence (GRADE)*
⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate
⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- These results apply to the use of emtricitabine/tenofovir as PrEP in men who have sex with men. It is reasonable to extrapolate these results to transgender women who have sex with men and sex workers, who were not explicitly included in the studies. This evidence does not apply as clearly to the use of tenofovir as monotherapy, given the low representation of this intervention in the trials. It does not apply to HIV uninfected men who have a serodiscordant stable male partner, since in this case it is more effective to treat the infected patient and achieve undetectable viral load to reduce HIV transmission than the use of PrEP.

About the outcomes included in this summary

- The selected outcomes are those considered critical for decision-making, based on the opinion of the authors of this summary. They agree with those presented in most systematic reviews identified.

Balance between benefits and risks, and certainty of the evidence

- Because it is an intervention with clear benefits and minimal to no adverse effects, the balance between benefits and risks is clearly favorable.

Resource considerations

- Tenofovir disoproxil fumarate costs between 2 and 5 dollars per pill, and emtricitabine/tenofovir (Truvada®) costs between 20 and 40 dollars per pill. So, a daily regimen with Truvada® costs between 7300 and 14600 USD per person per year.
- The FDA has already approved at least one generic alternative to Truvada® [30], which would lower PrEP costs.
- Reducing costs and implementing infrastructure and adherence programs that ensure maximum effectiveness are needed in order to maximize the cost-effectiveness of PrEP.
- It is reasonable to conduct a formal economic analysis in the places where this intervention is being considered, especially in places where the direct cost of the drug, or those derived from its implementation, are substantial.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary, most patients and physicians should lean in favor of its use.
- However, there are prejudices about the possibility that the use of PrEP would promote risky behaviors in men who have sex with men, although this has not been proven. This concern has permeated patients, and some see PrEP users as irresponsible. While this perception is probably changing rapidly, it is important to consider this factor.

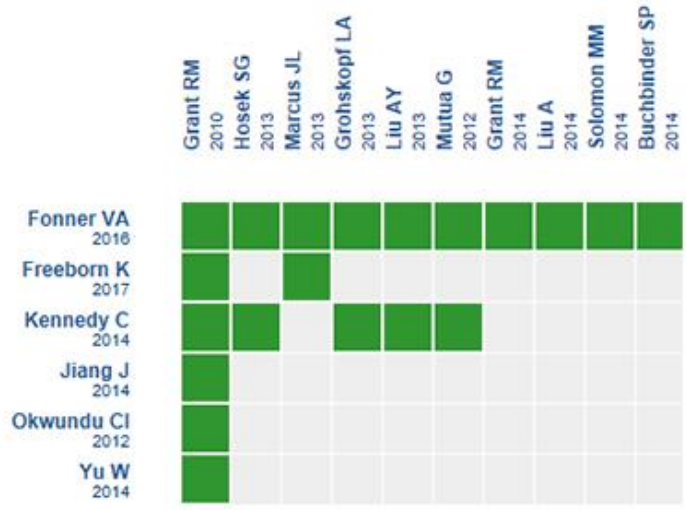
Differences between this summary and other sources

- The conclusions of our summary agree with those of most of the systematic reviews identified.
- The main clinical guidelines, such as the CDC [31] and the WHO PrEP implementation tool [32] highlight that emtricitabine/tenofovir is the approved PrEP formulation and that there is insufficient evidence to support the use of tenofovir disoproxil fumarate alone as prevention.
- The USPSTF is, as of December 2017, still in the process of giving a recommendation regarding PrEP [33].

Could this evidence change in the future?

- The likelihood that the conclusions of this summary about the effectiveness of oral PrEP is modified with future evidence is low given the high certainty of the existing evidence. The conclusions about changes in risk behaviors might probably change with new evidence.
- There are randomized trials evaluating the safety of a new formulation of tenofovir (tenofovir alafenamide with emtricitabine) [34] and at least one evaluating the effectiveness of a new injectable antiretroviral used as PrEP, cabotegravir, in trans women and men who have sex with men compared to emtricitabine/tenofovir [35].
- No new trials evaluating the use of monotherapy with tenofovir disoproxil fumarate in men who have sex with men were found.
- Several systematic reviews are in process evaluating different aspects of PrEP, such as cost-effectiveness [36],[37], its influence on sexual risk behaviors [38] and its effect on bone mineral density [39].

How we conducted this summary
Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Oral PrEP for prevention of HIV infection in men who have sex with men

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

Potential conflicts of interest
The authors do not have relevant interests to declare.

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