CONSENSUS DOCUMENT

PROPHYLAXIS PRE-EXPOSURE HIV IN SPAIN

NATIONAL PLAN ON AIDS
PREP EXPERT GROUP
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

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ABBREVIATIONS USED

QALY	Quality-adjusted life years
DALY	Years of life adjusted by disability Committee of
CHMP	medicines for human use Advisory and Advisory
COAC	Committee of NGOs Plasma viral load
CVP	
BMD	Bone mineral density
EMA	European Medicines Agency Estimated
FGe	glomerular filtration rate
FTC	Emtricitabine
MSM	Men who have sex with other men Sexually transmitted
ITS	infections
who	World Health Organization
UNAIDS	Joint United Nations Program on HIV and AIDS People who inject drugs
PID	
PIJ	Syringe exchange program National Plan on AIDS
PNS	
PPE	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
TAR	Antiretroviral treatment
TDF	Tenofovir disoproxil fumarate
HIV	Human immunodeficiency virus Hepatitis A
HAV	virus
HBV	Hepatitis B virus Hepatitis C virus
HCV	Human papilloma virus
HPV	

ABSTRACT

Introduction.

Pre-exposure prophylaxis (PrEP) is a biomedical intervention aimed at preventing the transmission of HIV in HIV-negative people at high risk of contracting the infection. The licensed combination is based on tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) in a single pill (Truvada®), once daily.

Aim.

Provide updated information on PrEP based on the scientific evidence published so far, formulating the criteria for the selection of people likely to receive it and assessing the possible models of service provision according to different healthcare organizations in our environment.

Methods.

This document, coordinated by the PNS, has been developed by a group of experts in different disciplines related to HIV who have worked at four levels: coordination, drafting group, review group and consultative group. We have worked with a mixed consensus methodology through face-to-face meetings with experts and rounds of exchange of opinions via e-mail. Once the document is finalized, it is posted on the web for comments.

Results.

Most studies have shown great variability in terms of its efficacy, close to 86%. These results are closely linked to the level of adherence to treatment. In our context, with an epidemic concentrated in MSM, PrEP is more cost-effective in high-risk MSM and should not be an isolated intervention but used in combination with other interventions. The use of PrEP involves clinical and analytical follow-up along with assisted counseling and adherence control. Most studies recommend monitoring for one year. Subsequently, they will assess the discontinuity of PrEP, plan a reevaluation, and establish referrals to community or support programs.

Conclusions.

PrEP must be prescribed in healthcare units that meet minimum requirements to guarantee the proper functioning of the intervention, although community centers could be incorporated into the recruitment of susceptible people for its use. The systematic implementation of PrEP should be accompanied by a monitoring and evaluation system with standardized common minimum information collection instruments and efficient information circuits. It is advisable to carry out cost studies that include the evaluation of adherence, the price of drugs and the capacity of the programs to ensure that the population receiving the intervention is adequate. Having local implementation feasibility studies can help you plan for PrEP.

ABSTRACT

Introduction.

Pre-exposure prophylaxis (PrEP) is a biomedical intervention aimed at preventing the transmission of HIV infection in HIV-seronegative people at high risk of infection. The authorized combination is based on tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) in a single tablet (Truvada®), once daily.

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Provide up-to-date information on the PrEP based on the scientific evidence published so far, formulating the criteria for selecting people likely to receive it and assess possible models of service delivery according to different healthcare organizations in our environment.

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Results.

Most studies have shown great variability in efficacy, close to 86%. These results are clo- sely linked to the level of treatment adherence. In our context, with a concentrated MSM epidemic, PrEP is more cost-effective in high-risk MSM groups and should not be an isolated intervention but used in combination with other interventions. The use of PrEP entails clinical and analytical follow-up along with counseling and adherence control. Most studies recommend monitoring for one year. Subsequently, the discontinuity of PrEP will be assesses, planning a re-evaluation and establishing referrals to community or support programs.

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PrEP must be prescribed in care units that meet minimum requirements to ensure the correct operation of the intervention, although in the recruitment of people who is susceptible to use community centers could be incorporated. Systematic implementation of PrEP should be accompanied by a monitoring and evaluation system with standardized minimum common information instruments and efficient information circuits. It is advisable to carry out cost studies that include the evaluation of adherence, the price of drugs and the ability of the programs to ensure that the population receiving the intervention is adequate. Having local implementation feasibility studies can serve to assist in the planning of PrEP.

CONTENTS

1. INTRODUCTION

Pre-Exposure Prophylaxis (PrEP) is a biomedical intervention aimed at preventing HIV transmission in HIV-negative people at high risk of contracting the infection. The regimen approved by the European Medicines Agency (EMA) consists of the daily use (one pill once a day) of an antiretroviral medicine (Tenofovir disoproxil fumarate (TDF) + Emtricitabine (FTC)) before exposure to the virus, and it must be accompanied by a package of preventive measures to improve adherence and influence the adoption of lower-risk behaviors.

PrEP, as a biomedical intervention, is one more preventive option to consider within the offer of combined prevention. It must be taken into account that biomedical interventions are influenced by factors related to human behavior [1] and therefore must be associated with other preventive measures that are collected, with a new approach, in combined prevention [two,] term that includes the synergy between behavioral interventions, biomedical, treatment and social justice and protection of rights. This change has been necessary, since there are no unique measures in prevention [3] and it has been found that interventions with modest levels of efficacy can increase it if they are combined with other [Four.]

Different modeling studies in the United States and the cost effectiveness of different prevention interventions, specifically biomedical and behavioral, in key populations, concluded that interventions aimed at promoting early HIV diagnosis, continuity of health care and treatment, had less cost than PrEP for each HIV infection averted. In addition, interventions targeting groups with high-risk practices, such as those associated with improving continuity of care and reducing the risk of HIV transmission, were generally more cost-effective [5.] In a review of studies on preventive strategies Jacobson and Walensky [6,] stated that most of them demonstrate the cost effectiveness of the interventions, however, not all of them were feasible [7, 8.]

Whether in clinical trials, pilot studies or in countries where PrEP is implemented, it is accompanied by other preventive interventions. Table 1 lists the main prevention strategies associated with PrEP.

Table 1. Strategies combined with PrEP

Strategies Change of behaviors	Strategies Biomedical	Strategies treatment	Strategies defense of Rights
Assisted Council for Early Diagnosis	PPE risk reduction HIV		Political leadership
Affective education-sexual	STI screening	ART at diagnosis	Participation community
Promotion of the use of condom	vaccination HAV, HBV and HPV	STI treatment	Access to services
Damage reduction: exchange of syringes and treatment opiate substitute			

Source: Own elaboration from [14].
STIs: Sexually Transmitted Infections. PEP: Post-exposure prophylaxis, ART: Antiretroviral treatment. HAV: Hepatitis A virus HBV: Hepatitis B virus HPV: Human Papillomavirus

In the use of combined prevention to reach the 90-90-90 goal, that is, to diagnose 90% of people infected with HIV, facilitate antiretroviral treatment (ART) to 90% of diagnosed people and obtain a 90% % undetectable viral load in people on ART, UNAIDS [9] recommends a 2-step approach to limiting the epidemic:

1. Increase the number of people taking the test.

two. Combine 2 or more preventive strategies, at least one that includes ART.

Although the studies conducted did not show evidence of risk compensation, results of the real-life implementation of PrEP in San Francisco found a relatively high incidence of STIs (particularly rectal) and a 41% reduction in use self-reported condoms among a subgroup of those taking PrEP [10].

The duration and design of the clinical trials carried out to date has not made it possible to assess risk compensation, although a high prevalence of

risk and STI practices in the PrEP user population [eleven]. In general, in terms of STIs, and given the short follow-up time of men who have sex with other men (MSM) users on PrEP in the trials, a significant increase in bacterial STIs, such as syphilis and gonorrhea, although it is true that PrEP users previously had very high prevalences [12]. Likewise, it has been described that individuals on PrEP report being more willing to have sex without a condom with an HIV-positive partner, having a greater probability of having 10 or more sexual partners, or having more receptive anal sex without protection [13].

In a meta-analysis conducted to evaluate the differences in STI acquisition among MSM, they showed that they were 25.3 times more likely to contract *Neisseria gonorrhoeae* Among those who used PrEP, 11.2 times more likely to contract *Chlamydia trachomatis*
and 46.6 times more likely to have a syphilis infection, compared to those who did not use PrEP [14].

However, it has also been described as an opportunity to increase STI screening, treatment and management, as PrEP is recommended as part of combination prevention that includes STI screening, risk reduction advice, and promotion of use. condom [fifteen].

Although there are issues that have not yet been fully clarified, it can be concluded that these data recommend the use of PrEP with TDF / FTC, in combination with other preventive strategies [10], in people at high risk of HIV acquisition and in the context of public health programs [16].

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2. OBJECTIVES

The purpose of this document is to provide up-to-date information on PrEP as a biomedical intervention aimed at preventing HIV transmission in HIV-negative people at high risk of contracting the infection. Based on the scientific evidence published so far, selection criteria will be formulated for people eligible for PrEP and possible models for the provision of the service according to different healthcare organizations.

3. METHODOLOGY

This document, coordinated by the PNS, has been developed by a group of experts in different disciplines related to HIV who have worked at four levels:

- **Coordination:** The PNS team has been in charge of coordinating the work, meeting the schedule, drafting and final acceptance of the document.

- **Writing group:** made up of experts who were in charge of writing the entrusted section, based on the available scientific evidence.

- **Review group:** experts from different disciplines who reviewed the document proposal prepared by the writing team.

- **Consulting group:** panel of agents involved in the response to the epidemic, made up of representatives of the regional HIV plans, the scientific societies related to HIV, the professional organizations involved and civil society represented through the NGO Advisory and Consultative Committee (COAC) , which has revised the document in order to obtain the maximum consensus between the different levels of participation.

In order to offer maximum transparency in the content of this document, it has been chosen to work with a mixed consensus methodology, through face-to-face meetings with experts and rounds of exchange of opinions via email, in which all the stakeholders have participated. groups of different levels of work. Throughout the entire process, the PNS has acted as the coordinating body, also providing technical and logistical support.

Finally, the document prepared was published on the PNS website with a deadline for public comments.

4. ANALYSIS OF THE CURRENT SITUATION

4.1. Review of the scientific evidence

Given the current situation of the epidemiological pattern of HIV at the international level, many studies have been carried out with the aim of finding new measures that help reduce the incidence of infection. To this end, different clinical trials have been launched on PrEP targeting MSM, discordant heterosexual couples, people who inject drugs (PID) and sexually active women. In most studies, the combination of TDF / FTC has been used in both daily and on-demand doses, but in some studies TDF has also been used exclusively.

Most of the studies have shown great variability in terms of its efficacy, depending on a multitude of factors, although, in two of them carried out in Europe, efficiencies close to 86% have been achieved. Likewise, their safety has been demonstrated, both in clinical trials and in observational studies launched in different countries (Table 2).

The results on efficacy are closely linked to the level of adherence to treatment, which entails the need for continuous monitoring and repeated preventive advice to enhance and facilitate said adherence.

The use of antiretroviral drugs can favor the appearance of adverse effects. The results presented so far demonstrate the need for close monitoring of people taking PrEP due to the potential decrease in both creatinine clearance [1,2] as of bone mineral density [3] (BMD), with statistically significant differences with respect to the control arm. The long-term impact of PrEP use in people without HIV infection is not yet known. The results of the different studies underway will provide an approximation that will allow the necessary measures to be established to minimize the presence of these effects.

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4.2. PrEP in the international context

Although PrEP has shown its efficacy in various clinical trials and pilot projects, to date its international implementation is scarce and there is still little information on its effectiveness and cost-effectiveness in real conditions of use.

The US Drug Agency (*Federal Drug Administration [FDA])* was the first to authorize the extension of the indication for Truvada® (TDF / FTC) to include PrEP in April 2012, so that today it is incorporated into the *US National HIV / AIDS Strategy*[1] published in July 2015, as one more component of prevention. Currently, other countries have approved this extension of the indication, or are in the process of doing so. However, the modalities in which clinical practice has been incorporated in each country in which the new indication has been authorized vary considerably, and in many of them governments do not cover the cost[2-5], as seen in table 3.

On July 22, 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)[6] issued a positive opinion to expand the indication of Truvada® in the EU as PrEP, in combination with other preventive measures and safer sexual practices to reduce the risk of HIV-1 infection in high-risk adults.

Following this positive opinion, on August 18, 2016 the European Commission[7] adopted the resolution modifying the marketing authorization for the drug Truvada® to include its use in pre-exposure prophylaxis. Next, the laboratory holding the authorization has to initiate the national procedures for each Member State to make a decision on price / financing and the conditions of effective use in the context of their health policies and services.

Currently, in Spain, the technical sheet for Truvada® as an ARV treatment for HIV, establishes a hospital use[8].

Table 3 shows the updated data as of December 2017. However, given that these data are constantly changing, it is advisable to consult other sources of information.

Table 3. Status of registration of Truvada® for use as PrEP in different countries

Included in the benefits		Not included in the benefits	
Country	Registration Status	Country	Registration Status
USES	Approved April 2012 Daily use	**Thailand**	Presentation for approval in 2014 Daily use
South Africa	Approved November 2015 Daily use	**Peru**	Approved April 2016 Daily use
Kenya	Approved December 2015	**Australia** Daily use	Approved May 2016 Daily use
Canada	Approved February 2016 Daily use	**Swiss**	Available one container monthly per person
Israel	Approved February 2016	**EU countries**	EU approved August 2016 daily use only: Germany, Austria, Bulgaria, Cyprus, Czech Republic, Croatia, Denmark, Slovakia, Slovenia, Spain, Estonia, Finland, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Poland, Portugal (two), UK(3), Romania and Sweden
France	EU approved August 2016 daily use only. Start January 2016 by Authorization Temporary Use for daily and intermittent use		
Norway	EU approved August 2016 daily use only. Start October 2016		
Belgium	EU approved August 2016 daily use only. Start June 2017 (1)		
Luxembourg	EU approved August 2016 only daily use. Imminent start.		

Source: self made. Table made as of December 2017.

(1) *Medication copayment € 11.90.*

(two) *Portugal: in May 2017 announced that it is studying the cost of withdrawing the healthcare copayment and establishing referral circuits for the implementation of PrEP.*

(3) *Scotland: approved for inclusion in the National Health Service benefits from April 2017 (Communication from the Scottish Medicine Consortium on April 10, 2017, implementation in 3-4 months).*

In any case, it cannot be ignored that people interested in its use, obtain it outside the formal circuit of public or private health in the countries. The most frequent forms used for uncontrolled access to PrEP are the repeated request for non-occupational post-exposure prophylaxis, sharing the drugs with HIV-infected people in treatment, and the purchase of generics on-line. In any of these cases, follow-up medical controls, adherence and adverse effects are not carried out, so it carries substantial risks [9].

Therefore, it is possible that the outlook could change significantly in the immediate future. [3] given that in addition to the clinical trials and pilot studies completed, there are about 16 studies pending final results and more than 27 studies underway or planned to start, which may yield new data [10].

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4.3. Cost-effectiveness studies

The availability of scientific evidence has favored the publication of guidelines recommending the use of PrEP [1-8]. In some of these guidelines or positions, the cost of PrEP is mentioned as an important factor to take into account, particularly in the case of its generalization. The WHO, in its consolidated guidelines of 2015, takes into account the financial implications in its recommendations and highlights the variability in the cost-effectiveness estimates of PrEP and its dependence on the price of the drug [Four.]

Given the strength of the evidence on its efficacy, the recommendations for its use and its recent approval by the EMA [9] It is essential to know the conditions in which this intervention would be cost-effective, the factors that exert the greatest influence on the cost-effectiveness and the budgetary impact that it could have.

In recent years, numerous cost-effectiveness studies have been published in various populations [10-15] and different regions [10-19]. Although the results of these differ based on the type of model used, the assumptions, the parameters and costs considered and the population studied, they can serve to obtain general conclusions and principles on the cost-effectiveness of PrEP that could be applied in our context.

Most studies have compared the costs and benefits of introducing PrEP or not and use various outcome indicators, such as HIV infections averted, QALYs (quality-adjusted life years), or DALYs (quality-adjusted life years). disability). In studies on PrEP in MSM, Chen and Dowdy estimate that PrEP is more cost-effective if used in groups with high prevalence and high adherence [8], but it decreases in groups of monogamous couples and in serodiscordant couples when the seropositive person follows ART. Other authors such as Ouellet et al. calculated that on-demand PrEP would save costs over a lifetime [10].

Taking into account the current costs of Truvada®, the implementation of PrEP would be cost-effective within 40 years or more. However, a decrease in its current cost of more than 80% would make PrEP a cost-effective intervention in 20 years [twenty.]

In studies carried out in serodiscordant couples, PrEP would be cost-effective in 20 years, but it has been shown that the use of condoms and treatment as prevention are more cost-effective [14].

In our context, with an epidemic concentrated in MSM, it is relevant that most authors report that PrEP is more cost-effective in groups of MSM with high-risk practices [17,21–24] and that it should not be an isolated intervention but rather used in combination with other interventions.

nes [22,25].

In conclusion, for PrEP to be cost-effective and even cost savings, there are a number of factors to take into account that have been highlighted in studies. The first is that its effectiveness depends significantly on adherence; second, the price of drugs would have to fall to be cost-effective in the medium term (<20 years) and third, the capacity of the programs to ensure that the population receiving the intervention is adequate (high incidences of HIV) .

It is therefore necessary to carry out cost studies that include this type of assessment and that allow recommending an eventual form of financing and implementation of this intervention. [26].

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5. ELIGIBILITY CRITERIA

The eligibility criteria must ensure the correct identification of people at high risk of HIV infection. These criteria must be adapted to the context of each country, however, according to epidemiological data, the group that would benefit the most from receiving PrEP in Europe is the group of MSM and transgender people, with a high risk of exposure to HIV, as already it has been explained in previous chapters.

Table 4 shows the different eligibility criteria for PrEP in MSM defined in the recommendations of the main international organizations and in some countries.

Table 4. Status of the international eligibility criteria for MSM

Organism	

CDC [1]	• MSM at substantial risk of contracting HIV:
	  • Sexual partner with HIV.
	  • Recent bacterial STI.
	  • High number of sexual partners.
	  • History of non-use or inconsistent use of condoms. Sex workers.
	  •

who [two]	• People at substantial risk of HIV infection (HIV incidence> 3%).
EACS [3]	• MSM or transgender people with inconsistent condom use with casual partners or HIV + partner without treatment, with recent STI or use of post-exposure prophylaxis.

ECDC [4]	• HIV negative MSM and transgender women clinically assessed as at high risk of contracting HIV based on the following criteria:
	  • Who report sex without a condom in the previous 3 months, and
	  • That they affirm probable repeated sexual intercourse without a condom in the next 3 months.
	• HIV-negative heterosexual men and women who are clinically assessed and considered to be at high risk for HIV.

ANRS [5]	• People> 18 years old, with negative HIV serological test, no signs of primary HIV infection, without recent exposure to HIV and with high risk of sexual acquisition of HIV: • MSM or transsexuals who have or have had anal sex without a condom with at least two different partners in the past 6 months, or STI episodes in the past 12 months, or multiple PEPs in the past 12 months, or used drugs during intercourse sexual. • "Special cases": Sex workers exposed to sex without a condom, people exposed to sex without a condom with partners from a population group with a high HIV prevalence: people from countries with high prevalence, people with multiple sexual partners, people injecting drugs (PID). • People who have sex without a condom with partners who have STIs, genital ulcers, or bleeding that may increase the risk of acquiring HIV. • People in other situations of high risk of acquiring HIV.

Source: own elaboration from [1-6].

The eligibility criteria established in Spain based on scientific evidence are detailed in Table 5.

Table 5. Eligibility criteria for MSM and transgender people

AND **n the MSM group:**
• To be over 18 years old • Rule out the existence of an HIV infection • At least two of the following high risk criteria for HIV infection: **to.** More than 10 different sexual partners in the last year. **b.** Unprotected anal sex in the last year. **c.** Drug use related to unprotected sex in the past year. **d.** Administration of post-exposure prophylaxis on several occasions in the last year. **and.** At least one bacterial STI in the past year.
In transsexual people who have high-risk sexual practices, the same criteria will be applied as for the MSM group.

Source: Own elaboration from [1-7].

Other key populations to consider, provided they are over 18 years of age and HIV infection has been ruled out, would be [1-7]:

1. PID and share injection equipment, included in syringe exchange programs (PIJ) and / or opiate replacement therapy (OST), and who have unprotected sex.

two. People who practice prostitution exposed to unprotected sex Highly vulnerable people:

3.

to. Unprotected sex in the last year with multiple different sexual partners and with ignorance of their serological status.

b. Unprotected sex in the last year with partners from population groups with high HIV prevalence (countries with high prevalence (> 1%), or with people who inject drugs).

c. With a history of ulcerative STIs in the last year.

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6. CONTROL AND CLINICAL MONITORING

Once the persons at substantial risk of HIV infection susceptible to PrEP have been identified, who accept the treatment and have no clinical contraindications for its administration, they will be informed of the necessary medical controls, of the adverse effects and they will sign the commitment to therapeutic adherence.

Before starting PrEP, the following tests should be done: [1,2]

to. HIV test: HIV serology with a fourth generation ELISA test and if there are symptoms or signs of primary infection, confirmatory tests will be carried out, in addition to a plasma viral load (CVP) of HIV. PrEP should not be started until HIV infection is ruled out.

b. STI screening: should include gonococcus, chlamydia, syphilis, in all people, even if they are asymptomatic. If an STI is detected, acute HIV infection should be ruled out before starting PrEP.

c. Hepatitis Serology:

- HAV: Screening is recommended to establish immunological status in persons susceptible to being vaccinated. That is, those who perform sexual practices that enable fecal-oral transmission (*Rimming* or anilingus).
- HBV: Vaccination is recommended if serology is negative or antibody levels are below the limit of protection. If you have an acute HBV infection, starting PrEP is contraindicated.
- HCV: If active chronic hepatitis C is diagnosed, PrEP will not be started until a full study of the situation is performed and the initiation of treatment for hepatitis C is considered.

d. Serum creatinine and phosphorus, estimated glomerular filtration rate (eGFR), routine urine analysis with glycosuria, sediment, and urine protein / creatinine ratio. TDF used in PrEP can be nephrotoxic and should not be used with eGFR <60 mL / min or with clinically significant proteinuria

and. Pregnancy test in fertile women.

6.1. Clinical Follow-up

After starting PrEP, a clinical and analytical follow-up must be performed every 3 months that includes: [1.2]

- HIV serology with a fourth generation ELISA and CVP if there are symptoms or signs of acute infection or another STI is diagnosed.
- STI screening.
- Serum creatinine and phosphorus, eGFR, urine system with glycosuria, sediment, and urine protein / creatinine ratio.
- Pregnancy test in fertile women.

6.2. Adverse effects

The drugs commonly used for PrEP are TDF / FTC. The safety of these drugs in the short and long term in HIV patients receiving antiretroviral treatment is well known. Information is being generated from different clinical trials on what happens when they are used for PrEP in people without HIV infection. [3.]

When TDF / FTC are used for PrEP their tolerability is generally good. During the first 4 weeks, gastrointestinal discomfort may occur, with worse digestive tolerability compared to placebo, especially nausea, which disappears later. [Four.] This can impact adherence and may even lead to withdrawal. Regarding other toxicities, decreases in glomerular filtration (eGFR) have already been observed in week 4, and in Bone Mineral Density (BMD) already in week 24, of little intensity, but statistically significant. [5.6.] These effects have no clinical relevance during the observation period and are reversible after stopping treatment.

Regarding long-term safety, data on renal and bone toxicity are already being generated, although a longer follow-up in cohort studies will be necessary to assess its true magnitude.

6.3. Adhesion control

Correct adherence is the fundamental factor for the effectiveness of PrEP, both to prevent new infections and to avoid the appearance of resistance in case of infection. This has been the reason for the failure of some clinical trials. Adherence to PrEP is higher in recent clinical trials, in their open-arm extensions, and in demonstration projects compared to early clinical trials [7]. Probably the reason is that the patient in real life is more motivated, knows the benefits and has decided to take it [8].

Although there are different possible guidelines, daily administration is probably easier to follow than intermittent.

Different strategies have been proposed to reinforce adherence to PrEP, always based on patient training, which include: complete information on PrEP (objective, how to take it, importance of adherence, potential adverse effects and their management, signs and symptoms of PrEP). acute HIV infection); mechanisms to establish routines that fit in with their work and social life; mechanisms and systems to avoid forgetting; monitoring of adherence at each visit; multidisciplinary assisted education and counseling [8].

There are various methods to assess adherence to PrEP, such as counting pills, dispensing through electronic pill cases, sending reminder messages via SMS, direct information from the patient or through questionnaires, tests on dried blood or hair. [7].

capillary blood samples or concentrations of the active substance in blood.

Pharmaceutical intervention at the time of dispensing is an important measure to reinforce adherence and monitor objectives in relation to pharmacotherapy and interactions with the different substances that patients consume.

6.4. Preventive advice for risk reduction

It is recommended to adapt models used in the diagnosis of HIV or in the counseling of infected people [9] and develop effective models that avoid risk compensation [10].

Key elements of risk reduction advice include [9]

- Create and maintain a climate of trust and confidentiality to discuss sexual behavior and substance abuse.
- Build a permanent dialogue with the patient about their risk practices and document them in the clinical report.
- Reinforce that PrEP is not always effective in preventing HIV, but that its consistent use in conjunction with other prevention measures offers a very high level of protection.

Before starting PrEP:

- Ensure that the patient understands its operation, risks, benefits and need for adherence [eleven].
- Report preferably in the patient's native language, avoiding technicalities [10].
- Determine your suitability through a risk assessment through interviews or computer tools [9].
- Maintain an interactive style tailored to each patient [two].
- Inform about complementary harm reduction strategies and the need to use condoms to reduce the risk of acquiring an STI.

After starting PrEP, follow up every 3 months [2.11]

for:

- Monitor the presence of high-risk behaviors and receive advice to reduce them,
- Confirm and reinforce the use of condoms.
- Discuss the use of other contraceptive methods.
- Assess substance use and mental health, if indicated.
- In patients with partners with HIV, without ART, the initiation of ART in the partner should be recommended, at each visit [eleven.]
- For patients who remain at high risk or who need additional prevention services, refer to more intensive intervention programs.
- With PID, provide sterile material or refer to a Drug Dependent Care Center and / or syringe exchange points (PIJ) [eleven.]

Annually:

Discuss discontinuation of PrEP. In that case, plan a reevaluation and make referrals to community or support programs.

6.5. Duration of PrEP

The fundamental limitation to define it is that there is little experience on it in the long term: most of the published studies report follow-up of around one year [2, 8-11.]

It must be reassessed periodically and suspended in the following circumstances: by decision of the patient, by abandonment of follow-up, by disappearance of risk practices, by appearance of serious kidney, bone, digestive toxicities, or of any other type considered important,

due to acute or chronic HBV infection, due to chronic poor adherence despite repeated attempts to improve it, or due to acquisition of HIV infection, or a treatable infection [2,8-11]. Once suspended, it is important to record the HIV status at that time, the reasons for dropping out, adherence and risk practices in the medical history.

Table 6 summarizes the recommendations for control and clinical follow-up.

Table 6. Summary of Recommendations for Control and Clinical Follow-up

1.	Before starting PrEP, HIV infection, STI screening, hepatitis virus serology, blood and urine tests, and pregnancy tests should be ruled out.
two.	After starting PrEP, an HIV test, STI screening, blood and urine tests, and a pregnancy test should be performed every 3 months.
3.	Monitor during the follow-up of PrEP the potential clinical and analytical adverse effects of the drugs used and the possible drug interactions that favor renal dysfunction.
Four.	Monitor and reinforce adherence at each PrEP follow-up visit.
5.	Perform assisted risk reduction counseling before starting PrEP and after starting it, quarterly, at each follow-up visit.
6.	Reassess PrEP at each follow-up visit.
7.	Suspend PrEP in cases of abandonment of follow-up, poor adherence, serious adverse effects, disappearance of risky practices or acquisition of HIV infection.

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7. PROVISION OF THE SERVICE

The physician should recommend and monitor PrEP as part of an active risk reduction intervention that includes health education and promotion of safe sex. People receiving PrEP must be and remain actively involved in risk reduction intervention and take responsibility for proper adherence to PrEP. It must be ensured that PrEP is prescribed in healthcare units that meet certain minimum requirements to guarantee the correct functioning of the program, although community centers could be incorporated into the recruitment of susceptible people for its use:

to) For the control and clinical follow-up and for the dispensing of the medicine, the Hospital Units for HIV Infection, STI and HIV Centers or Sexual and Reproductive Health Centers.

b) For the identification and detection of susceptible candidates and to provide the advice assisted at the beginning of the same and during the follow-up, the Primary Care Centers, the STI and HIV Centers and the Community Centers.

Regardless of the physical space or organic or institutional affiliation, these healthcare units should meet the following requirements:

- Presence of medical professionals with the necessary training in HIV infection, antiretroviral treatment and other STIs.
- Have the necessary devices to make an adequate initial evaluation and follow-up (exclude HIV infection and other STIs, examinations to evaluate the toxicity of the medication and the selection of resistances, in case an infection occurs).
- A hospital pharmacy service for the custody, dispensing and monitoring of the use of medication.
- Capacity and training to carry out assisted and repeated preventive counseling in adherence and sexual health.

In relation to the drug used, it should be taken into account that Royal Decree 1345/2007 [1] It details in its article 24 the conditions of prescription and dispensation of the

drugs for hospital use, and specifies in section 3 that certain drugs will be subject to restricted medical prescription when they are reserved for treatments that can only be used in hospitals or authorized healthcare centers, due to their pharmacological properties, their novelty or due to public health reasons.

Likewise, the considerations of the technical sheet must be taken into account [two] of the drug. All drugs authorized for the treatment of HIV infection are subject to restricted medical prescription and are considered drugs for hospital use, as stated in section 4.2 of their technical sheets. *"Treatment should be started by a doctor with experience in treating HIV infection."*

Ideally, all conditions should be specified in a single center, although if necessary or convenient, it could be the result of an agreement between two or more centers. The centers participating in PrEP programs can be varied and adapt to different realities, however, the classification of hospital use of the medication used for PrEP must be taken into account, which could condition the user uptake circuits, follow-up of the same and the dispensing of the medication, which will always have to be linked to a hospital center.

It should be remembered that in Spain, health care in the SNS is the responsibility of the Autonomous Communities, therefore, they are the ones that will be able to decide the centers that could provide the service and the circuits, provided that they meet the requirements for dispensing. of PrEP.

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8. MONITORING AND EVALUATION

For all the above, the introduction and systematization of PrEP in the NHS would entail logistical and organizational challenges, added health costs and some other aspects that should be known, monitored and evaluated by the administrations responsible for public health. Having local implementation studies available can help with planning [1-3].

In this context, the systematic implementation of PrEP should be accompanied by a monitoring and evaluation system with standardized common minimum information collection instruments and efficient information circuits.

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9. CONCLUSIONS AND RECOMMENDATIONS

HIV PrEP is a biomedical intervention aimed at preventing HIV transmission in HIV-seronegative people at high risk of contracting the infection and therefore should be treated as one more public health intervention, which should be integrated into prevention strategies combined, including not only biomedical interventions, but also behavioral and treatment strategies and rights that include access to services.

It is important to remember that efficacy results from clinical trials cannot be extrapolated to reality without real-world effectiveness data available. Furthermore, it is necessary to take into account the determinants of effectiveness, such as lack of adherence, and the possible adverse effects of the interventions, among which are the increase in higher-risk practices and the consequent increase in other STIs.

In general, the criteria for use, coverage and adherence are the factors that can most influence the effectiveness of a biomedical intervention; in addition to cost-effectiveness.

recommendations

1. PrEP is one more preventive option, within the offer of combined prevention. In our context, with an epidemic concentrated in MSM, PrEP would be more cost-effective in high-risk groups of MSM and should not be an isolated intervention but rather used in combination with other interventions. PrEP should not be started until HIV infection is ruled out.

two. The eligibility criteria must ensure the correct identification of people at high risk of HIV infection. These criteria must be adapted to the context of each country, however, the group that would benefit the most from receiving PrEP in Europe is the group of MSM and transgender people, at high risk of exposure to HIV.

3. PrEP must be prescribed in healthcare units that meet minimum requirements to guarantee the proper functioning of the program, although community centers could be incorporated into the recruitment of susceptible people for its use.

Four. Based on the available scientific evidence, the daily dose of the combination of tenofovir and emtricitabine (TDF / FTC) is that authorized by the EMA. TDF used in PrEP can be nephrotoxic and should not be used with eGFR <60 mL / min or the presence of clinically significant proteinuria.

5. The results on the efficacy of PrEP are closely linked to the level of adherence to treatment, which entails the need for continuous monitoring and repeated and adapted preventive advice that enhances and facilitates said adherence.

6. After starting PrEP, a clinical and analytical follow-up should be performed every 3 months that includes HIV serology with a fourth-generation ELISA and PVC if there are symptoms or signs of acute infection or another STI is diagnosed. The follow-up requires not only the evaluation of the toxicity of the medication, but also the monitoring of HIV infection and infection by other STIs, the evaluation of adherence and assisted counseling.

7. Most studies recommend a one-year follow-up after which, discontinuation of PrEP will be assessed, a reevaluation will be planned, and referrals will be made to community or support programs. Once suspended, it is important to record the HIV status at that time, the reasons for dropping out, adherence and risk practices in the medical history.

8. In relation to assisted counseling for risk reduction, it is recommended to adapt models used in the diagnosis of HIV or in the counseling of infected people and to develop effective models that avoid risk compensation.

9. The implementation of PrEP should be accompanied by a monitoring and evaluation system with standardized common minimum information collection instruments and efficient information circuits. Likewise, it is advisable to carry out cost studies that include the evaluation of adherence, the price of drugs and the capacity of the programs to ensure that the population receiving the intervention is adequate.

10. Having local implementation studies available can help you plan for PrEP.

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