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HIV pre-exposure prophylaxis (PrEP): strategy with future?

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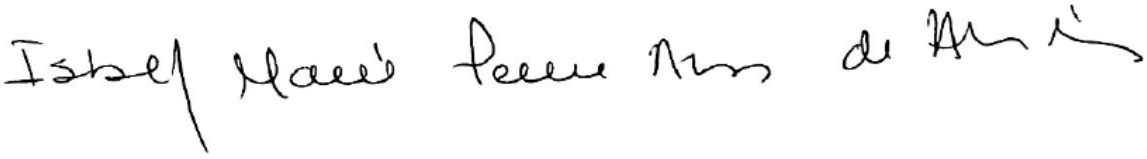

Assinatura do Coorientador

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DEDICATÓRIA

À minha família, pelo incansável apoio ao longo de todo o meu percurso.

Aos meus amigos, por me acompanharem nestes seis anos e por os tornarem especiais.

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RESUMO

Introdução: Atualmente, estima-se que ocorram, globalmente, cerca de dois milhões de novas infeções pelo Vírus de Imunodeficiência Humana (VIH) por ano, apesar de décadas de Terapêutica Antirretroviral (TARV) de alta eficácia. Como tal, novas estratégias preventivas devem ser desenvolvidas de forma a impedir a progressão desta epidemia. A profilaxia de pré-exposição (PrEP) consiste num método biocomportamental que combina uma abordagem farmacológica com estratégias de promoção de comportamentos sexuais saudáveis. É dirigida a indivíduos com alto risco de adquirirem a infeção por VIH, como homens que têm sexo com homens (HSH), casais heterossexuais serodiscordantes, mulheres transsexuais, homens e mulheres heterossexuais que não usem o preservativo frequentemente e cujos parceiros sexuais sejam de alto risco, e utilizadores de drogas injetadas. Vários estudos randomizados foram realizados e demonstraram que a PrEP é uma medida segura, bem tolerada e eficaz na redução do risco de aquisição da infeção por VIH.

Objetivos: O objetivo principal desta revisão bibliográfica é a análise da literatura mais recente relativa à PrEP, focando-se nos seus benefícios, desvantagens e desafios à sua implementação, procurando entender se é uma estratégia preventiva com futuro.

Métodos: Uma pesquisa inicial foi efetuada no *PubMed* com recolha de artigos escritos em inglês e português no período entre 2011 e 2017. Apenas os que continham informação relativa aos tópicos abordados nesta revisão foram selecionados, tendo sido feito um esforço para usar a literatura mais recente (de 2016 a 2018). Adicionalmente, algumas notícias da internet, comunicados de imprensa e relatórios foram citados por referirem importantes desenvolvimentos relacionados com a PrEP.

Discussão: Apesar de a PrEP ter evidência como uma medida preventiva eficaz, a sua implementação encontra-se num impasse e a sua utilização pelos indivíduos está aquém da esperada. Alguns fatores contribuem para isto, nomeadamente a compensação do risco, com consequente elevação da incidência de infeções sexualmente transmissíveis (ISTs), custo, estigma, falta de conhecimento da população sobre a PrEP e insegurança dos profissionais de saúde.

Conclusão: Superar estas adversidades deve ser um objetivo atual. Governos e legisladores devem investir em formas de reduzir o custo da PrEP, aumentar o conhecimento da sua população alvo com medidas de sensibilização e realizar ações de formação aos profissionais de saúde, para evitar o estigma e desmistificar mitos e ideias erradas. Só enfrentando estas barreiras é que a PrEP pode ser implementada totalmente e conseguirá atingir o seu potencial preventivo.

Keywords: HIV infection; HIV prevention; Pre-exposure prophylaxis (PrEP); Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination

ABSTRACT

Introduction: Currently, it is estimated that there are approximately two million new Human Immunodeficiency Virus (HIV) infections worldwide each year, despite decades of Highly Active Antiretroviral Therapy (HAART). It seems that new prevention efforts should be made in order to halt the spread of this epidemic. Pre-exposure prophylaxis (PrEP) is a bio-behavioral preventive method that combines an innovative pharmacologic approach with strategies to promote healthy sexual behaviors. It is aimed for individuals at high risk of becoming infected with HIV, such as men who have sex with men (MSM), heterosexual discordant couples, transgender women, heterosexual men or women who infrequently use condoms and have sex with partners with high risk of HIV infection, and injecting drug users. Various randomized placebo-controlled studies were reviewed and demonstrated that PrEP was a safe, well-tolerated and effective way of reducing the risk of acquiring HIV infection.

Objectives: The main objective is to review the recent literature regarding PrEP, focusing on its benefits, disadvantages and potential risks and the challenges to its implementation, and to understand if it is an effective preventive strategy with future.

Methods: An initial search was conducted in *PubMed* that gathered articles, written in English and Portuguese, within a time period from 2011 to 2017. Only the articles containing information about the main topics covered by this review were selected and an effort to cite the most recent ones (from 2016 to 2018) was made. Additionally, a few web news as well as press releases and reports were cited as they contained information regarding recent developments on PrEP.

Discussion: Despite the evidence that PrEP is an effective preventive strategy, its implementation is at a standstill and its uptake is not as expected. Some factors have contributed to this, namely risk compensation with consequent rise in incidence of sexual transmitted infections (STIs), cost, stigma, low awareness and insecurity of health professionals.

Conclusion: Addressing these barriers should be the focus now. Policy makers and governments should invest on ways to reduce the cost of PrEP, raising its awareness and on training for health professionals, while also fighting stigma and debunking myths and false ideas. It is only by tackling these barriers that PrEP can be fully implemented and reach its preventive potential.

Keywords: HIV infection; HIV prevention; Pre-exposure prophylaxis (PrEP); Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination

LIST OF ABBREVIATIONS

ART - Antiretroviral Therapy

BMD - Bone Mineral Density

BTS - Bangkok Tenofovir Study

CDC - Centers for Diseases Control and Prevention

eGFR - Estimated Glomerular Filtration Rate

EMA - European Medicines Agency

FDA - Food and Drug Administration

FTC - Emtricitabine

HAART - Highly Active Antiretroviral Therapy

HBV - Hepatitis B Virus

HIV - Human Immunodeficiency Virus

INFARMED - Instituto Nacional da Farmácia e do Medicamento

iPrEx - Preexposure Prophylaxis Initiative Trial

iPrEx-OLE - Preexposure Prophylaxis Initiative Trial - Open-label Extension

MSM - Men Who Have Sex With Men

PrEP - Pre-Exposure Prophylaxis

RCTs - Randomized Double-Blind Placebo Controlled Trials

STIs - Sexual Transmitted Infections

TDF - Tenofovir Disoproxil Fumarate

TDF-FTC – Combination of Tenofovir Disoproxil Fumarate/Emtricitabine

UK – United Kingdom

UNAIDS - Joint United Nations Programme on HIV/AIDS

USA – United States of America

WHO - World Health Organization

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INTRODUCTION

The global prevalence of Human Immunodeficiency Virus (HIV) infection has increased over the years due to the efficacy of the *"Highly Active Antiretroviral Therapy"* (HAART), which has allowed HIV-infected patients to live longer. Contrastively, the global incidence has decreased. Recent data shows up to two million new HIV infections occur yearly worldwide. While it is true that this percentage of new infections has decreased since 2010, most likely due to global efforts made to strengthen the HIV treatment and prevention strategies, the rate of decline is disappointing.[1]

In this context, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and its partners established a new set of goals - 90-90-90 - to be reached until 2020: "90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy (ART) and 90% of all people receiving ART will have viral suppression".[2]

Efforts to fight this epidemic should be made and preventive measures assume a key role in this. The pre-exposure prophylaxis (PrEP) is a preventive strategy that consists in the administration of an antiretroviral combination to individuals at high risk of becoming infected with HIV, such as men who have sex with men (MSM), heterosexual discordant couples, heterosexual men and women who engage in sexual risk behaviours (such as condomless sexual practices) and whose sexual partner is at high risk of HIV infection, and injecting drug users. It also acts as a behavioural strategy by promoting healthy practices, such as condom use, and discouraging risky ones, like multiple sexual partners and needle sharing.

In 2012, the U.S. Food and Drug Administration (FDA) approved a fixed-dose oral antiretroviral combination tablet containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) (TDF-FTC) as a once-daily regimen of PrEP[3]. This approval emerged from reports of numerous randomized placebo-controlled studies which demonstrated that this PrEP regimen was a safe, well-tolerated and effective way to reduce the risk of acquiring HIV infection [4-11]. Four years later, the European Medicines Agency (EMA) granted a marketing authorization of TDF-FTC for PrEP[12].

However, in the past few years, the PrEP implementation has not been very successful. Some reasons can be attributed to this, such as stigma, low awareness and lack of engagement in medical community. Additionally, concerns regarding its adherence-dependent efficacy, high cost, fear of side effects, drug resistance, as well as the potential to lead to risk compensation, have also been a challenge to the implementation of PrEP.

OBJECTIVES

The main objective is to review the recent literature regarding PrEP, focusing on its benefits, disadvantages and potential risks and challenges to its implementation. It aims to understand if it is truly a necessary, cost-effective and important preventive strategy.

METHODS

The first step was to conduct an online broad search in *PubMed*, using the *MeSH* keywords: HIV infection; HIV prevention; Pre-exposure prophylaxis (PrEP); Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination. A temporal window from 2011 to 2017 was selected, excluding articles prior to this. Out of the articles available, only those written in English and Portuguese were selected. After designing a layout of the review and the topics it would cover, the following articles were selected: the main studies regarding PrEP's efficacy as well as articles with information about epidemiology, pharmacology, side effects, implementation and its barriers, clinical guidelines. As the review went on, there was a need to use bibliography that dated previously to 2011, mostly from 2010 and a few from 2009, as they contained important information that needed to be cited. After a thorough analysis, an effort was made to cite the most recent literature, from 2016 and/or 2017, as this being a topic with constant updates, a review without recent references could lead to outdated information, compromising its objectives. Also, only a few systematic reviews were analysed with the rest being majorly original articles. In addition, press releases, reports and web news were also used as they provided information regarding recent advances, namely PrEP policies and measures in specific countries and cities around the world.

DISCUSSION

A PROPHYLACTIC STRATEGY WITH ANTIRETROVIRAL THERAPY

The current approved regimen of PrEP consists of an antiretroviral combination tablet containing TDF and FTC. Both drugs are nucleotide reverse transcriptase inhibitors that have been used in the treatment of HIV infection for over ten years and have a well-studied and favourable safety profile.[3,12,13]

In the event of intolerance or toxicity to FTC, monotherapy regimen with TDF can also be used. Topical preparations are still being studied as potential alternatives for oral intake, allowing individuals to choose the administration method that best fits them and with which they can achieve high adherence rates.[13]

Pharmacological properties and side effects

According to pharmacologic studies, TDF can reach elevated levels in the rectal mucosa, thus providing protection for the individuals who are at risk of acquiring HIV infection by the practice of receptive anal intercourse. The FTC can achieve high concentrations in the female genital tract, which contributes to the prevention of HIV transmission in women.[14,15]

The TDF-FTC combination has been associated with side effects, such as increases in serum creatinine and decreases in bone mineral density (BMD)[16,17]. In fact, according to the published guidelines an estimated glomerular filtration rate (eGFR) below 60 mL/min is a contraindication for PrEP initiation[18,19].

Another possible occurrence is a flare of hepatitis B in patients with chronic hepatitis B virus (HBV) infection. The TDF is considered a first-line treatment for chronic HBV. In patients with HBV who do not require treatment but are taking PrEP, the discontinuation of TDF could theoretically result in a flare. In this sense, testing for the presence of HBV should be considered in candidates for PrEP.[20]

Another possible side effect is the development of drug resistance in individuals taking PrEP that unknowingly have HIV infection[21]. The two most important mutations are the M184IV, associated with FTC, and the K65R mutation, associated with TDF. The first one causes high-level resistance to FTC and increases susceptibility to TDF. Interestingly, the M184IV mutation reduces viral fitness, with plasma levels of HIV-1 RNA lower than a wild-type virus (no mutations). However, its effect on drug resistance surpasses this positive

effect on viral replication. The K65R mutation is the second most common mutation and leads to intermediate resistance to both TDF and FTC.[13,22]

CLINICAL TRIALS

Animal studies

Numerous animal trials were important as they established the efficacy and safety of TDF-FTC long before human trials began. In humanized bone marrow-liver-thymus mice, it was demonstrated a reduction in intra-vaginal, intravenous and rectal transmission of HIV infection after pre-treatment with systemic TDF and FTC alone or TDF-FTC[23,24]. In primates, administration of oral PrEP or topical tenofovir-based gel, prior to systemic or mucosal simian HIV challenge, was shown to provide substantial protection[25,26].

In light of these findings, clinical trials started to be conducted in order to evaluate the efficacy and safety of TDF-FTC in humans.

Human studies

Several randomized clinical studies have emerged in these past few years and have demonstrated that PrEP is a well-tolerated, safe and effective way to decrease the risk of acquiring HIV infection among high-risk individuals (*Table I, Appendix*).

Men who have sex with men and transgender women

Three several large trials have demonstrated the efficacy of PrEP in MSM and transgender women.

The iPrEx[5] study demonstrated a 44% (95% CI, 15-63) reduction in the incidence of HIV infection in MSM and transgender women on a daily-oral TDF-FTC regimen. This value was lower than what was hypothesized, mostly due to lack of adherence and low drug plasma levels[5]. However, in patients with detectable TDF-FTC plasma levels and high adherence, it increased to 92% (95% CI, 40-99), showing a possible dose-effect relationship and that the efficacy of PrEP was adherence-dependent[5]. An open-label extension (iPrEx-OLE) to this study helped to support these findings by showing a 90% reduction in the incidence of HIV infection in individuals with detectable TDF-FTC levels, consistent with a use of two/three tablets per week, thus confirming the dose-effect relationship previously mentioned[9].

Other two studies, IPERGAY[10] and PROUD[11], focused only on MSM. The IPERGAY study was the first to test the efficacy of a sexual activity-dependent or on-demand PrEP

regimen, in which patients took two pills of TDF-FTC up to 24 hours before sexual intercourse and two more after (24h and 48h after, respectively)[10]. The results showed a reduction in the incidence of HIV infection of 86% (95% CI, 40-98), one of the highest values encountered to date[10]. Although the results were promising, they seem to be valuable only for an uptake of at least fifteen pills per month. A more intermittent uptake would not deliver the same results[10]. An open-label extension to this study yielded similar results: this regimen continued to be effective as long as the individuals adhered sufficiently to it, its safety profile was favourable and the use of PrEP reduced the fear and more pleasure was experienced in sexual relationships[27].

In PROUD, the first open-label randomized trial, MSM received daily TDF-FTC either immediately (immediate group) or after a period of one year (deferred group)[11]. It showed a reduction in the incidence of HIV infection of 86% (90% CI, 64-96), a value that, just like the IPERGAY study, exceeded others encountered in previous trials[11]. These efficacy findings were reported early and obtained during a follow-up period of only one year (deferred phase) in which only the immediate group had access to PrEP[11]. However, after observing an alarming high incidence of HIV infection in the deferred group, it was decided to offer PrEP to the deferred group and initiate a new long-term follow up of around two to four years (post-deferred phase)[28]. Recent data, presented in *9th International Acquired Immunodeficiency Syndrome Society (IAS) Conference (2017)*, showed promising results: the immediate group, that had been receiving PrEP before, maintained a stable incidence of HIV infection, indicating that this preventive effect was durable; in the deferred group, a significant decrease in HIV infection was noted after PrEP was delivered[28].

Heterosexual men and women and serodiscordant couples

Two large randomized double-blind placebo-controlled trials in Africa have yielded results for heterosexual men and women and serodiscordant couples.

The TDF 2 study in Botswana, in which HIV-seronegative heterosexual men and women either received daily TDF-FTC or placebo, demonstrated a reduction in the incidence of HIV infection of 62% (95% CI, 22-83). A limitation to this study hinges on the fact that the rate of study completion was lower than predicted, with most participants withdrawing from the trial. However, the authors believe that, since these rates were similar in both study groups, they did not affect the findings.[7]

In the PARTNERS-PrEP study[6], the HIV-1 seronegative partner from a serodiscordant couple was randomly assigned to receive one of three regimens: once-daily TDF, TDF-FTC or placebo. The results observed were a 67 % reduction in the incidence of HIV infection in the TDF group (95% CI, 44-81) and 75% in the TDF-FTC (95% CI, 55-87),

with the protective effects of either regimen alone not being significantly different[6]. When it comes to HIV serodiscordant couples, both PrEP and ART are recommended and effective preventive strategies. Hence, preventive approaches that combine these two options are beneficial since together they appear to be more effective than as stand-alone alternatives[6]. In this context, an open-label demonstration project, called Partners Demonstration Project[29], was conducted and it consisted of integrated ART and PrEP delivery to serodiscordant couples. The HIV-infected partners received ART while the uninfected ones were offered PrEP until their infected partner had been on ART for six months, a time deemed necessary to achieve a viral suppression state. This way, PrEP would be used as a bridge to ART[29]. They showed that the combination of these two strategies led to virtual elimination of new HIV infections, with an incidence reduction of 95% (95% CI, 87-98), and demonstrated that "PrEP as a bridge to ART" was a very effective preventive strategy in serodiscordant couples[29].

Heterosexual women

Overall, the results of trials revolving exclusively around heterosexual women have been controversial and not as promising as others that focused on other groups, including heterosexual couples.

In the CAPRISA 004 trial, women were instructed to apply one dose of a 1% tenofovir vaginal gel or placebo within twelve hours before or after sexual intercourse. The incidence of HIV infection was reduced by 39% (CI 95%, 6-60) and this reduction began as soon as the gel started being applied and reached a peak of 50% after twelve hours. Much like previous findings, this rate was increased with higher adherence.[4]

The FEM-PREP study, in which the participants were assigned either daily oral TDF-FTC or placebo, demonstrated no significant reduction in the incidence of HIV infection, with value in the TDF-FTC group of 6% (95% CI, -52-41). The occurrence of side effects was significantly higher in the TDF-FTC group which led to higher rates of drug discontinuation in this group. The adherence was low with less than 40% of participants with evidence of recent pill use. Due to this, the study was stopped early.[30]

The VOICE study[31] evaluated the efficacy of oral TDF alone and TDF-FTC as well as vaginal tenofovir-gel compared to oral placebo pill and placebo vaginal gel, respectively. The reduction in the HIV incidence was of -49% (95% CI, -129-3) for oral TDF group, -4% (95% CI, -49-27) for oral TDF-FTC and 14,5% (95% CI, -21,39) for tenofovir gel[31]. There was no statistically significant difference in the rate of this incidence between a group receiving any study product and its respective placebo group[31]. Some explanations for the disparity in these results have been hypothesized. Firstly, as mentioned before, the efficacy

of PrEP is strongly influenced by the adherence rate and in women the adherence assumes an even more significant role[30]. According to pharmacokinetic studies, the threshold of adherence needed to obtain sufficient levels of tenofovir in vaginal tissue is higher than the one in rectal tissue, meaning that women who engage in vaginal intercourse must adhere to a stricter regimen that is less-forgiving of imperfect use and requires more doses per week[32]. In these two studies that yielded no results, the adherence rate was lower than expected, which could be a strong reason for that. Secondly, some biologic factors should also be mentioned, such as high cytokine level in the vaginal tissue that could impair the effect of vaginal tenofovir preparations[33]. Lastly, behavioural factors like stigma and low awareness of the risk could also have contributed to low adherence to PrEP and, thus, to the acquisition of HIV infection[30,34,35].

Injecting drug users

The Bangkok Tenofovir Study (BTS) evaluated the efficacy of daily oral use of TDF in injecting drug users. It observed a 49% reduction in the incidence of HIV infection (95% CI, 10-72), becoming the first study to show the effectiveness of oral tenofovir use in prevention of HIV infection in this high-risk group[8].

Side effects and adverse events

Overall, the reported side effects in the clinical trials encompass the following: gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea)[5-8,10,11,30,31], non-specific symptoms (headache, arthralgia, rash)[5-8,10,11,30,31], constitutional symptoms (anorexia, weight loss)[5-8,10,11,30,31], laboratory abnormalities (elevations in serum creatinine[5-8,10,11,30,31], alanine aminotransferase[8,30]), changes in bone mineral density and bone fractures[7, 10]. Across all studies it was observed no significant difference between the study groups in the frequency of deaths, serious clinical or laboratory adverse events[5-8,10,11,30,31].

The most commonly reported drug-related symptoms were the gastrointestinal manifestations, particularly nausea and vomiting, which were characterized as being mild, transient and more frequent during the first month of follow-up, resolving thereafter. These symptoms were described as more frequent in the TDF-FTC group than in the placebo group.[5-8,10,11,30]

The TDF treatment is known to cause increases in serum creatinine and in some studies[5,30,31] these effects seemed to occur more in the TDF-FTC group. Most creatinine elevations were self-limited, mild and with no clinical significance[5,30,31]. In one study, FEM-PREP, these renal effects were more prominent in the TDF-FTC group, requiring discontinuation of the drug, in about 5% of the participants[30].

Other laboratory abnormalities, like alanine aminotransferase elevation, were detected and described as mild and not clinically significant and appeared to be more frequent in the TDF-FTC group, albeit less frequently than other manifestations.[8,30]

In addition, the TDF can also lead to changes in BMD and thus to bone fractures. Overall, those alterations, when detected, were similar between the TDF-FTC and placebo groups[7,10], except in the TDF-2 trial[7]. During its two years of follow-up, the T and Z scores for BMD declined at the forearm, hip and lumbar spine in TDF-FTC study group. In contrast, the rates of bone fractures were similar in both groups[7]. One could explain these findings with the fact that half of the participants already had low BMD before the start of the study and therefore could have been at increased risk for loss of BMD while taking the drug[7].

The effects on pregnancy are also a concern. Both TDF and FTC are reported to be safe and are considered pregnancy category B drugs, meaning animal reproduction studies have failed to demonstrate a risk to the fetus and there are no well-controlled studies in pregnant women[36]. The trials reported no difference between groups in the risk of adverse pregnancy-related events[6,30]. However, drug was discontinued once pregnancy was confirmed, therefore it was not possible to assess the effects of PrEP throughout pregnancy[6,30]. A different study that evaluated these effects on the participants of the PARTNERS trial also found no difference between study groups[36].

Drug resistance

One of the disadvantages of PrEP use is its potential to lead to drug resistance, particularly when its intake occurs between acquisition of HIV infection and its diagnosis.[37]

Data from the clinical trials demonstrated that the occurrence of resistance is possible, albeit rare, with the mutation M184IV being the most common, followed by mutation K65R[5-7,11,30,31]. These resistances were mostly limited to individuals who were retrospectively found to have been assigned PrEP during unrecognized and seronegative acute HIV infections[5-7,11,30,31]. Therefore, the resistances that emerged were due to this failed recognition of an acute HIV infection, allowing these individuals to be incorrectly exposed to PrEP.

One could say that these trials had limitations[37]. First, their methods of testing detected only resistant variants that existed at high frequencies (>20%)[5-8], failing to identify those that were present in lower frequencies which have been proved to also lead to failure of treatment later on[38,39]. Second, most HIV acquisition happened due to absence of PrEP intake and exposure, which is the main factor that contributes to the development of this resistance[40]. Therefore, it is not surprising that the number of resistances detected was low.

A recent study was undertaken, in which a highly sensitive testing was performed among HIV seroconverters within the Partners-PrEP trial. The main aim was to detect low frequency resistance that could have not been detected by the standard testing. With this new method, they were able to conclude that resistance at low frequency was present in individuals with PrEP intake between the acquisition of HIV infection and the discontinuation of PrEP. Its results were important by showing that, in some of these individuals, this resistance developed in breakthrough infections - infections that arose after random assignment, during a period of PrEP use. It also reported that this occurrence may be more common with a regimen of TDF-FTC than TDF alone, owing to the FTC-selected mutation M184IV.[37]

Fortunately, the overall drug resistance that was detected is still much lower than the one estimated by mathematical models. As demonstrated across the clinical trials, high adherence and consistent PrEP use is effective and the acquisition of HIV infection happened in individuals who most likely were not taking PrEP, during HIV seroconversion, therefore leading to a very low risk of resistance associated with consistent PrEP use.[37]

BARRIERS AND CHALLENGES TO THE IMPLEMENTATION OF PREP

Despite the favourable results from numerous clinical trials, PrEP uptake has been disappointing. In the United States of America (USA), ever since its approval, in 2012, the uptake has been low, and although it has been increasing over time, there is still a long way to go. Back in 2015, the Centers for Diseases Control and Prevention (CDC) estimated that PrEP was indicated for about 1,2 million people. However, recent reports say that, in 2017, there were only about 125000 active PrEP prescriptions[41]. For this reason, some authors have characterized PrEP as being a “boutique intervention” that fails to achieve the public health impact to protect these high risk populations from acquiring HIV infection[41].

Numerous studies and surveys have identified some barriers to this implementation such as risk compensation, cost, low awareness, low risk perception, stigma, fear of side effects, and health professionals’ insecurity.

Risk compensation

The risk compensation, also known as behavioural disinhibition, consists of an increase in risk behaviour due to an exaggerated feeling of safety from PrEP, such as decrease in condom use, with consequent increase in STIs, as well as needle sharing, in the case of injecting drug users. This phenomenon has been used by some organisations

in their campaigns against PrEP as its main argument, and has become an important barrier to its implementation.[42]

To assess this phenomenon, the clinical trials evaluated the occurrence of these behavioural changes. All the participants were offered condoms, safer sex counseling and other information regarding risk behaviors and, throughout the follow-up, they were regularly questioned about risky sexual practices as well as condom use. All in all, there was no risk compensation observed and no difference between study groups[5-8, 10, 11, 30, 31]. Some trials even reported an increase in condom use, decrease in the number of sexual partners and, in the case of the BTS study[8], an additional decrease in needle sharing. The rate of STIs was moderately high in some studies but no difference was observed between study groups, supporting the initial observation that the intake of PrEP did not lead to risk compensation[5-8, 10, 11, 30, 31].

One should look at these data and remember that the PrEP clinical trials, apart from the PROUD study[11], were randomized double-blind placebo controlled trials (RCTs). The RCTs are not adequate to evaluate risk compensation, since participants are unaware whether they are receiving PrEP or placebo, and therefore have more concerns regarding risk and are more cautious[43]. In this way, experts worry that this phenomenon may occur outside the clinical trial context. For this purpose, open-label studies which are not blinded and the participants know what type of medication they are assigned, as well as demonstration projects, are more useful to evaluate this as they closely resemble a real-world scenario[44,45]. The PROUD study, an open-label trial, showed no difference in the rate of STIs between the study groups. However, it also found that the participants allocated to the immediate group reported more condomless receptive anal sex with ten or more partners, in comparison with the other study group.[11]

In the open-label extension of the IPERGAY trial[27], it was observed that the probability of condom use decreased with increased risk perception, which could lead to increases in STIs. This did not affect the incidence of HIV infection as greater PrEP use in these individuals compensated for their low-level of condom use[27]. While a few of these findings can be alarming, some authors also note that the general increase in the prevalence of STIs over the years and its intensive screening in the clinical trial setting can play a role in the higher STIs rates detected[46].

Cost

The cost of the TDF-FTC has been indicated as a major obstacle to implementing PrEP. Its current price is high and without cost-sharing programs it could fail to achieve the

desired impact on public health and worsen health disparities by protecting only those able to afford it.[44]

Currently, in the USA, without financial funding, the cost is approximately 1500$ per month. This does not include additional expenses for screening, monitoring, regular physician visits and support that these individuals would have to go through[44,47]. Contrastively, in France, the cost is 500€ per month but it is reimbursed by the public health system. However, the baseline screening and monitoring tests cost an extra 200€ approximately, with only around 60% of it being refunded.[48]

A recent model of cost-effectiveness on MSM in the USA revealed important findings[47]. It reported that the presence of one of these conditions would improve PrEP's cost-effectiveness: higher adherence and therefore efficacy; a drop in drug prices of at least 80%; or a population's prevalence of HIV infection of over 20%[47]. In a high-adherence and high efficacy setting, PrEP would be cost-effective and cost-saving, meaning that by preventing HIV infection and reducing the need for lifelong HIV treatment, PrEP would give more money back to the healthcare system than its initial cost. It also found that risk compensation is a fourth factor with a strong negative influence on the cost-effectiveness of PrEP. For example, with a 25% of risk compensation, not even an 80% price reduction would lead to cost-effectiveness. Furthermore, if the PrEP efficacy were to be moderate (a reduction of incidence of HIV infection around 35%), the presence of risk compensation would actually lead to loss of money. However, in scenarios with high adherence and efficacy (92% reduction in incidence of HIV infection), PrEP would be cost-effective despite the presence of risk compensation.[47]

Despite these promising results on MSM, a recent analysis estimated that in injecting drug users, at the current price, PrEP is not likely to be cost effective and that other preventive strategies (like opioid agonist therapy, needle and syringe programs and HIV testing and treatment) could obtain the same or surpass the benefit achieved with PrEP alone at a substantially lower cost.[49]

Awareness

Even with an increase in publicity and media campaigns, low awareness of PrEP, by the individuals who would benefit most from it, is one of the main factors that has slowed down the implementation of PrEP.

In a study conducted in USA, in 206 patients, only 15% had any knowledge about PrEP. When informed about it and its efficacy, around 92% said they would likely or very likely discuss the possibility of using it[50]. Another study evaluated the knowledge of 209 MSM regarding PrEP and showed disappointing results, with majority of them reporting having little knowledge of PrEP and less than half reporting any interest in learning more about it[51]. A different one that focused on MSM of low and middle-income countries revealed that awareness of PrEP among them was generally low with an average of 29,7% (95% CI: 16.9–44.3)[52]. These findings are consistent with previous ones which revealed that individuals, at high risk, who were not part of PrEP trials had limited knowledge of it[52,53].

When comparing PrEP's targeted high-risk individuals, one study showed that PrEP awareness was affected by ethnicity and partner type, in which black and hispanic partners, and heterosexual partners were reported to have lower awareness, when compared to white partners and MSM, respectively.[54]

In contrast, in most of these studies, the willingness to use PrEP was found to be high, once these individuals became aware of it and its benefits. However, this eagerness does not correlate well with the actual use and intake of PrEP by individuals, as shown by some observations in USA cities, which cited that despite over half of MSM mentioned being keen to use PrEP, only 4% actually used it[55]. Willingness to use PrEP may not accurately predict actual acceptance since that is heavily influenced by individual factors and the context in which PrEP is provided[52]. Another explanation can be the fact that being a preventive strategy, the benefits of PrEP are not perceptible or noticeable to the individuals. Thus, it is difficult to convince them to adhere to this strategy unless they actually see themselves at risk of HIV infection.[56]

Risk perception

Another important factor that could impair PrEP's implementation is the perception of HIV infection risk by the PrEP candidates, which is often low, as seen in a study conducted in Canada[57]. In this study, 420 MSM were interviewed to assess their risk perception and compare it to an objective risk measurement using a validated index (HIV Incidence Risk Index for Men who have Sex with Men – HIRI-MSM). The results showed that while 64% of the participants were classified as high-risk by the objective measurement, only 27% perceived themselves as having moderate-to-high risk of HIV infection[57]. Additionally, it reported that the individuals with perception of high risk were more likely to use PrEP[57], a finding that has been documented in different studies[58,59]. Contrastively, other ones reported that individuals with low risk perception were less willing to use PrEP[60,61].

Stigma

Stigma towards HIV infected individuals is also a major issue that stalls the implementation of PrEP and can keep them from using it due to shame or fear of discrimination. In a recent study, it was reported that MSM expect some degree of stigma towards HIV infection or use of PrEP from their peers and relatives[52]. Another study, in which 50 individuals at high risk of HIV infection were questioned about their views on PrEP, found that while some saw it as an effective preventive measure, others saw it as a way to promote unacceptable social behavior and promiscuity[62].

Fear of side effects

The fear of side effects is also a concern for the individuals[52]. However, as mentioned before, the side effects that were most commonly associated with PrEP were moderate, disappearing after the first two months, and the rate of serious adverse events was low.

Health professionals' insecurity

Some of these obstacles are also present in the medical community. Although most professionals are aware of PrEP, some mention that additional training is needed, specifically on identifying potential PrEP candidates and on its prescription process. This way, they could feel more comfortable and more prepared to manage these situations. This training would be beneficial not only for the infectious diseases specialists, but also for generalists since they are the primary health figure to whom most uninfected-HIV individuals reach out to.[63,64]

Stigmatization from the physicians is also an issue that could damage PrEP's implementation. It can generate distrust in the patient-doctor dynamic and prevent future PrEP candidates to reach out to their clinicians.[52,56]

CURRENT STATUS

In the past few years, various organisations launched campaigns to promote PrEP and raise its awareness. Global and national websites have been created to inform the public about PrEP, containing fact sheets, essential information and promotional videos. Summits, conferences and meetings have been held in multiple countries with the aim of promoting the implementation and roll-up of PrEP. Clinical guidelines and national recommendations have been published as countries begin to approve PrEP.

Clinical guidelines

In May 2014, two years after PrEP's approval by the FDA, the CDC published the first practice guidelines recommending PrEP with the use of daily oral TDF-FTC.[18]

The World Health Organization (WHO) published recommendations for PrEP back in 2012, reviewing them in 2016, which are similar to the CDC ones, with the exception of recommending the use of TDF alone.[65]

Parallelly to this, it is estimated that there are around twelve additional national guidelines, a number that keeps increasing as more countries begin to approve PrEP.[66]

Approach to a patient with indication for Pre-exposure Prophylaxis according to Central for Diseases Control and World Health Organization guidelines[18,65]

Prior to initiation

In all potential candidates for PrEP, prior to the administration, it is necessary to assess their risk of HIV acquisition. For that purpose, a detailed sexual history should be collected with information regarding sexual acts (condomless penile-anal or penile-vaginal sex), number of partners and possible STIs over the last six months. A STI screening should be performed, including serologic testing for syphilis, gonorrhea and chlamydia. Drug use behaviors should also be assessed, namely the type of drug injected and the possibility of needle sharing.

After assessing the risk of HIV acquisition, the next step would be to evaluate the risk of treatment. This encompasses:

- The HIV serostatus (ideally no more than 7 days before starting PrEP) with a fourth generation antigen/antibody test. Additional HIV RNA test should be performed in individuals with symptoms suggestive of acute HIV infection;
- Serum creatinine should be measured to exclude patients with an eGFR lower than 60 mL/min;
- Testing for HBV infection with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) and hepatitis B surface antibody (anti-HBs). Patients should be vaccinated against HBV if the tests reveal absence of prior infection;
- History regarding risk factors for osteoporosis. A routine bone density screening is still not recommended and its benefit is unclear;
- Pregnancy test.

It is also important to assess the willingness to adhere to PrEP and possible barriers should be pointed out and discussed.

After all of this and if the individual is to be considered a candidate for PrEP, administration should be started 7 to 21 days before intercourse or other high-risk behaviors.

Contraindications

The PrEP is not to be initiated in the following situations:

- An individual with a positive or unknown HIV serostatus;
- Presence of symptoms or/and signs of acute HIV infection;
- An eGFR below 60 ml/min;
- Inability to adhere to the PrEP regimens and lack of social support or caretaker;
- Hypersensitivity to the active ingredient or/and excipient of TDF-FTC.

Monitoring

Monitoring patients during PrEP use is extremely important. One month after initiation, evaluation for side effects, adherence and presence of risk behaviors should be done. Every three months thereafter, the previous measures should be repeated with the addition of a HIV serostatus testing, serum creatinine measurement, STIs screening and pregnancy test. In each contact with the PrEP users, the clinicians should use motivational interviewing techniques to improve adherence, and should offer counseling on risk-reduction, reinforcing the importance of condom use and other preventive measures.

Suspension

The PrEP should be suspended in the presence of a diagnosis of HIV infection, renal or bone toxicity, lack of adherence, lack of high-risk behaviors that require the use of PrEP or in pregnant women with low HIV risk.

Reality in the United States of America

Although the uptake of PrEP has experienced a slow rise, one can assume that PrEP has partly contributed to the decrease in the annual number of new HIV infections observed in USA (10% between 2010 and 2014).[67]

Some states of the USA have shown impressive results. In 2010, San Francisco launched a "Getting to Zero" campaign with the aim of having zero new HIV infections, zero HIV-associated deaths and zero HIV stigma and discrimination in the city. In the next few years, the annual number of new HIV infections decreased to 329 in 2014 and reached a record low of 223 in 2016[68]. Similarly, in the same year, in New York, it also reached a record low of 2279, representing an 8,6% one-year decline[69].

While this is not present in all states, efforts are being made to achieve this. For example, Florida, that had the third-highest rate in 2016[70], is planning to offer PrEP for free statewide as part of a national preventive strategy.[71]

Reality in Europe

Even though the global trend shows a decline in new HIV infection cases, that has not occurred in Europe. In 2014, the number of annual new diagnoses was the highest since reporting started back in the 1980s. Within Europe, there are differences between the Western and Eastern regions. In the first, MSM are responsible for most of the increase in new HIV infections, whereas in Eastern Europe it is injection drug users and women who contribute to it the most. Another reason for these disparities in Europe hinges on the fact that public health services differ substantially: some countries have free HIV and STI testing and treatment services, others only have access to them at the expense of significant copayments and a few struggle to find health services that are confidential and free of prejudice. On top of that, funding for prevention is still a challenge. When some of the treatment goals are far from being reached, it becomes harder to motivate governments to implement and invest on PrEP.[48]

Nevertheless, in 2015, the efficacy results of two European clinical trials – PROUD[11] in United Kingdom (UK) and IPERGAY[10] in France – helped to build momentum for the implementation of PrEP in Europe[72]. A year after, the European Medicines Agency (EMA) granted a marketing authorization of TDF-FTC for PrEP[12]. This was an essential step as it contributed to the acceleration of PrEP's approval in European countries.

Recently, two demonstration projects in Amsterdam (AMPrEP) and Antwerp (Be-PrEP-ared) have been launched with the goal of providing useful information that could help shape national and European guidelines, furthering PrEP's implementation and its integration in the current prevention strategies.[72]

Although some progress has been observed in Western Europe, the Eastern countries lag behind. Therefore, supporting these countries and their demonstration projects and other national endeavors will be extremely important.[48]

France

France has been in the vanguard when it comes to PrEP in Europe. It was the first country from European Union to approve Truvada® (TDF-FTC) to be used as pre-exposure prophylaxis. Although it had not been approved by the EMA at that time, a recommendation for temporary use was granted. The drug would be fully reimbursed by the healthcare system, although follow-up visits and testing would only be partly refunded (60% of the costs). This was a major step in PrEP's implementation as it arose from combined efforts of society and the French government[48]. Another breakthrough was the approval and distribution of generic forms of the drug, thus lowering its cost and making it more cost-effective[73].

United Kingdom

As of this moment, in the UK, the PrEP medication is free, funded by the National Health System, only in Scotland and Wales[74]. In England, it is subjected to a three-year implementation trial (PrEP IMPACT), that will offer PrEP to approximately 10000 individuals. By addressing relevant questions about delivering PrEP on a large scale, this trial aims to help funders and policy makers to fully implement it in England[75].

Some recent epidemiologic data appears to be hopeful. In 2016, the UK witnessed a substantive decline in HIV diagnoses, especially in the high-risk group of MSM, that has been associated with a steady increase in the number of HIV diagnoses in the past. Aside from increases in HIV testing, improvements in the uptake of ART and sustained high condom use, the acquisition of PrEP through the internet was cited as a big contributor to this.[76]

Portugal

Within the Western Europe, Portugal has one of the highest incidences of HIV infection in comparison to the average European incidence. Although a decrease in the incidence has been observed throughout the years, some risk groups continue to have alarming rates that justify the need of improved preventive strategies.[77]

In this way, in November 2017, the Direção-Geral da Saúde (DGS) published a clinical guideline concerning the free access to PrEP. High-risk individuals who fulfill specific criteria (*Table II, Appendix*) should be referenced to a specialty consultation, to be scheduled in the maximum time of thirty days. Before initiating PrEP, the individuals must undergo clinical and laboratory evaluation (*Table III, Appendix),* risk counseling and health education regarding HIV infection, ISTs and contraception. Compared to other guidelines, this one offers the possibility of choosing a daily TDF-FTC regimen or an on-demand one

(*Table IV, Appendix*), allowing the individual to pick the one that suits them better and that will provide the highest adherence. Similarly to previous guidelines, suspension of PrEP should occur in the following situations: diagnosis of HIV infection, renal or bone toxicity, pregnancy in women that appear to have low risk of HIV acquisition, lack of adherence and when the risk behaviors that prompted the PrEP intake are no longer present.[19]

Currently, PrEP is being administered through an early access program, while the funding process is still being concluded. This program offers PrEP up to 100 individuals. These individuals must be referred through a public consultation specific of PrEP and each doctor must contact the pharmaceutical company (*Instituto Nacional da Farmácia e do Medicamento – INFARMED)* for each patient that qualifies for PrEP use, with a maximum of 5 requisitions in one submission. The INFARMED must then validate or not the request and communicate their decision to the hospital in 72 hours. A second consultation must then be scheduled, no more than 7 days after the initial one, and, if the request was validated and all of the laboratory testing that is necessary prior to the initiation of PrEP is done and there are no contraindications, PrEP can be discharged right away.[78]

As of now, four hospital, two in Lisbon (*Centro Hospitalar Lisboa Ocidental – Hospital Egas Muniz* and *Centro Hospitalar Lisboa Central – Hospital Curry Cabral*) and two in Porto (*Centro Hospitalar de São João* and *Centro Hospitalar do Porto*), have already launched their PrEP consultation and seem to be ready to start this early access program. This is a great step in the implementation of PrEP, as strategies like these contribute to a global and equitable access to PrEP and the health assistance that it requires.

RECOMMENDATIONS

EFFORTS TO IMPLEMENT PREP AND TO HELP REACH ITS FULL POTENTIAL

The current literature regarding PrEP is vast and new information and discoveries are being published. However, some of this literature has mostly focused on MSM and sexual discordant partners. Future research should be encouraged and efforts should be done to also focus these studies in women and injection drug users, populations that lack sufficient evidence or that have shown conflicting results, as discussed above. Investigation on long term safety is also important, particularly on renal and bone toxicity and the effect of TDF-FTC on pregnancy.

However, investing on research is not enough. Some challenges and barriers continue to stall PrEP's implementation and attention should be directed at so that they can be properly addressed.

The risk compensation has been largely advocated as one of the main concerns of PrEP. Although a consistent condom use can be difficult, it is still an easily available, cheap and effective measure against both STIs and HIV infection. Therefore, strategies to reaffirm this pivotal role of condoms should be adopted and certain messages should be transmitted: PrEP should not be seen as a replacement of condom but rather as an addition to it; PrEP does not protect against STIs; thus, a combination of these two provides the safest protection against both HIV and STIs.[79]

It also becomes important to think of strategies to tackle the cost and the issues surrounding it. Investors and policy makers need to be informed that it has been predicted that PrEP intake can lead to an estimated saving of 20,500 euros per a HIV infection that is prevented[80]. Alternatively, efforts to reduce the cost should be done by encouraging the development of generic forms of the drug. Recently, the FDA granted *Teva Pharmaceuticals* the right to produce generic *Truvada*®[81].

There is also a great value in educational strategies to improve PrEP awareness and reiterate its potential in the prevention of HIV infection. The way this information is provided to the individuals should be thoroughly investigated to sort out the most effective methods, whether through healthcare providers, print media and media campaigns, or more innovative methods, like social media and online dating applications. It is also important to have a better understanding of the relationship between willingness to use and the uptake of PrEP in "real word" scenarios. This way, effective policies can be developed to overcome this, facilitating the implementation of PrEP worldwide.[52, 82]

Stigma associated with HIV infection and discriminating attitudes towards potential PrEP users are still a major issue and barrier. Therefore, implementation strategies should not only focus on improving knowledge and awareness but also on reducing stigma. This not only applies to the general population, but also to the medical community, in which these issues are still very much present. It is crucial to sensitize these professionals, reduce the stigma and foster a friendly and positive relationship between them and future PrEP users[52,56]. Additionally, training and prescription tools are useful by helping the physicians to better manage the administration of PrEP. In fact, in the USA, some prescription tools are already available, such as PrEPline, a support hotline for clinicians, or a checklist to use before prescription, like the Truvada Checklist for Providers[82].

Ergo, investment now should be focused on how to tackle these issues head-on so that we can ensure an equitable and universal access to PrEP, allowing it to fully reach its potential as a preventive strategy.

CONCLUSION

The PrEP is a preventive strategy with future that has been shown to be effective, cost-effective and well-tolerated. It aims to help reduce the prevalence and incidence of HIV infection and the burden of the disease that comes from the intensive therapy the HIV infected individuals go through, this way improving the quality of life of these individuals and their partners.

One can say that this PrEP debate closely mirrors the one had years ago regarding the contraceptive pill. Some of the concerns voiced back then resemble the ones now and the issues and barriers to the implementation also have similarities. So, it is fair to say that while the PrEP debate is still in the beginning, and some questions still need to be addressed, it is still a preventive measure with great future potential, just like the contraceptive pill had back then.

As we speak, discoveries and new solutions are being investigated worldwide. Topical delivery methods are being tested and may present as a solution for the individuals who struggle with oral intake of a pill. Similarly, the on-demand regimen of PrEP is gaining more and more evidence to support its use as it could also improve the adherence rates and thus its efficacy.

The main message that should be taken from this review is that PrEP should not be considered a stand-alone preventive measure, as it is not sufficient nor cost-effective. However, combined with the promotion of other well-established and effective measures (such as condom use), it becomes an important additional strategy in the prevention of the HIV infection. In order to achieve that, PrEP needs to be fully implemented worldwide. Offering it to the individuals is simply not enough when they are unaware of it, when they are discriminated or when the physicians lack the training necessary to correctly manage them. Overcoming these barriers is nothing short of difficult but it is a vital step in the implementation of PrEP, and thus in the prevention of this epidemic that is the HIV infection.

APPENDIX

Table I - Summary of the results of the main PrEP randomized clinical studies

Clinical study	Year of publication	Population	Drug	Administration	Study subjects that contributed to analysis	Incidence of HIV infection Reduction (IR) (CI 95%)	Adjusted IR in individuals with high adherence (CI 95%)
CAPRISA 004 [4]	2010	Heterosexual women	TDF gel	Topical Within 12h before or after sexual intercourse	889	39% (6-60)	54% (4-80)
iPrEx [5]	2010	MSM and transgender women	TDF-FTC	Oral Daily	2499	44% (15-63)	92% (40-99)
Partners-PrEP [6]	2012	Heterosexual men and women	TDF-FTC	Oral Daily	4747	75% (55-87)	90% (58-98)
			TDF	Oral Daily		67% (44-81)	86% (67-94)
TDF 2 [7]	2012	Heterosexual men and women	TDF-FTC	Oral Daily	1200	62% (22 - 83)	-
FEM-PrEP [30]	2012	Heterosexual women	TDF-FTC	Oral Daily	2056	6% (-52 – 41)	-
Bangkok Tenofovir Study (BTS) [8]	2013	Injecting drug users	TDF	Oral Daily	2411	49% (10-72)	70% (2-90)
VOICE [31]	2015	Heterosexual women	TDF-FTC	Oral Daily	4969	-4% (-49 – 27)	-
			TDF	Oral Daily		-49% (-129 – 3)	-
			TDF gel	Topical Daily		14,5% (-21 – 39)	-
IPERGAY [10]	2015	MSM	TDF-FTC	Oral On-demand	400	86% (40-98)	-
PROUD [11]	2016	MSM	TDF-FTC	Oral Daily	523	86% (CI 90%, 64-96)	-

Table II - Criteria to identify individuals at high-risk of HIV infection that are potential PrEP users (according to the National Portuguese DGS recommendations)[19]

Sexual intercourse without consistent condom use in the last six months in one of the following conditions: 1. Sexual partner with unknown HIV serostatus; 2. Diagnosis of an STI.
Individuals whose partner is HIV infected, without treatment or medical vigilance or has viral suppression and who does not have consistent condom use;
Individuals who refer the use of recreational drugs during sexual intercourse;
Injection drug users who share needles or syringes;
Serodiscordant couples in a preconception situation or pregnancy.

Table III - Clinical and laboratory evaluation before prescribing PrEP and during follow-up (according to the National Portuguese DGS recommendations)[19]

Clinical evaluation	**Before prescription**	**First follow-up at 4th week**	**Subsequent trimestral follow-ups**
HIV and STD risk evaluation	✓	✓	✓
Development of a prevention plan for HIV and STIs	✓	✓	✓
Promotion of condom use	✓	✓	✓
Evaluation of the individual's knowledge about PrEP, motivation and adherence capacity	✓	✓	✓
Assess other medication for the possibility of drug interaction	✓	✓	✓
In fertile women, assess for pregnancy intent	✓	✓	✓
Assess for possible comorbidities and their risk factors (renal disease, bone disease and hepatitis B)	✓	✓	✓
Assess and treat concomitant diseases	✓	✓	✓
Assess drug toxicity and side effects		✓	✓
Laboratory testing			
Test for acute HIV infection with HIV RNA if patient has symptoms consistent with acute HIV infection or has had a high-risk exposure in the last 4 weeks: 4th generation serologic HIV test (Antibody anti-HIV1/2 + Ag p24)	✓	✓	✓
Hemogram, renal function, electrolyte panel and urinalysis	✓	✓	✓
STD screening (Syphilis, Chlamydia and Gonorrhea)	✓		✓
Pregnancy test	✓		✓
Serologic testing for hepatitis A, B and C	✓		

Table IV - PrEP regimens recommended (according to the National Portuguese DGS recommendations)[19]

TDF/FTC (200 mg + 245 mg), oral, 1 x day
TDF/FTC (200 mg + 245 mg), on-demand: 2 pills between 2 to 24 hours before exposure + 1 pill each 24 hours until the last exposure. Recommended not to exceed the maximum of 7 pills per week.
TDF monotherapy (200mg), oral, 1 x day, in the presence of intolerance or toxicity to FTC
In individuals with chronic hepatitis B, it should be prescribed TDF/FTC continuously

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