REVIEW ARTICLE

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HIV Pre-Exposure Prophylaxis in Central and Eastern Europe-Gains and Challenges in An Ever-Changing World

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ABSTRACT

Pre-exposure prophylaxis (PrEP) is an effective prevention tool for controlling the HIV epidemic. Since its approval in the United States in 2012 and Europe in 2016, it has become available on a global scale offered as a registered strategy in clinical studies or demonstration projects with a slow and steady increase. In the second quarter of 2022, PrEP became available in 78 countries globally, with around 3 million people having started using PrEP. Europe has been much slower than the rest of the world to roll out PrEP; nevertheless, currently, PrEP is nationally available and reimbursed in 21 countries; generics are available but not reimbursed in 14 countries. PrEP is not formally implemented in 20 countries, which are mostly Central and Eastern European countries. There are significant disparities between countries in terms of PrEP availability, accessibility, and usage, most likely due to social, cultural, and political differences. The major barriers to PrEP use are reported to be lack of knowledge of people in need, not being reimbursed, and low perception of HIV. PrEP uptake globally and regionally still lacks the power to have an impact on controlling the epidemic. High prioritization of PrEP targets will offer us a realistic chance of reaching the Joint United Nations Programme on HIV/AIDS (UNAIDS) goal of a 90% reduction in HIV infections by 2030 compared to 2010.

Keywords: pre-exposure prophylaxis, Central Europe, Eastern Europe, HIV infection, prevention

INTRODUCTION

It has been more than a decade since the first evidence of oral pre-exposure prophylaxis (PrEP) in the "Iniciativa Profilaxis Pre-Exposición" (iPreEx) study, which reported 44% efficacy (1). Following these results, the US Food and Drug Administration (FDA) approved PrEP in 2012 as a method of prevention from HIV for individuals at high risk (2), and two years later, the Centers for Disease Control and Prevention (CDC) published the PrEP guidelines (3). Then, many other randomized controlled studies followed (4-8). Although efficacy estimates in clinical trials seem to vary from 50% to more than 85%,

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analyses looking at drug levels reveal that adherence is linearly related to the level of protection, with efficacy rising to 90% with high adherence (4-6). The promising results of the "Intervention Préventive de l'Exposition aux Risques avec et pour les Gays" (IPERGAY) study (8) led France to start offering PrEP in November 2015 with reimbursement (9). European Medicine Agency (EMA) approval was received a year later (10). Following this, other European countries joined in, and PrEP availability in Europe showed a slow but steady increase.

CLINICAL AND RESEARCH CONSEQUENCES

PrEP was also proved highly effective in real-world settings. In Australia-New Wales, HIV incidence dropped to 1/1000 person-years (PY) between 2016 and 2018 compared to an expected incidence of 20/1000 PY (11). New HIV diagnoses in London showed a 32% decrease between 2015 and 2016 compared to the previous year (12). In San Francisco, the number of HIV diagnoses was reduced by 50% from 2013 to 2018 (13). Despite initial concerns for the likelihood of behavioral disinhibition due to PrEP use leading to an increase in sexually transmitted infections (STIs) and the development of drug resistance in case of suboptimal adherence, PrEP proved to be an effective tool with negligible adverse effects (14).

Studies from different parts of the world showed that PrEP, especially when used concomitantly with other interventions, was highly effective in reducing new HIV diagnoses and in fact achieved the most rapid decrease (15-18).

Since its approval PrEP has become available on a global scale and has been offered as a registered strategy or in clinical studies or demonstration projects with a slow and steady increase. In the second quarter of 2022, PrEP had become available in 78 countries globally, with around 3 million people on PrEP (19).

UNAIDS set fast-track targets in 2014 to reduce new HIV infections and AIDS-related deaths to less than 500,000 by 2020 (20). In addition, 3 million people were expected to have started using PrEP by 2020, with the aim being zero new infections and deaths by 2030 (21). However, in September 2020, UNAIDS announced that although there has been significant improvement, especially in antiretroviral treatment initiation and viral load suppression within the last decade, the 90-90-90 targets would be unmet (22). Despite all promising results, PrEP has not been approved in many countries resulting in a lower-than-expected uptake and in the last quarter of 2020 only around one million people were reported to be on PrEP (19). In 2019 UNAIDS announced that similar to the 90-90-90 targets, the PrEP target would also be unmet (23).

The situation in the European region was almost identical to the global picture. According to the European Centers for Disease Prevention and Control (ECDC) 2020 report, the number of new diagnoses had increased by 19% during the last decade, and although the European Union (EU)/European Economic Area (EEA) countries were quite close, the target would not be met for the European Region (24). The recent decline in the 2021 report is thought to be due to reduced testing and not a real decline (25).

Since the PrEP roll-out in France the introduction of PrEP in Europe has been much slower than in other regions and Europe comprised only 7% of global PrEP initiations in the last quarter of 2020 (19). Currently, PrEP is nationally available and reimbursed in 21 countries and generics are available but not reimbursed in 14 countries. PrEP is not formally implemented in 20 countries, which are mostly Central and Eastern European countries (26). Reports from the European region call attention to significant regional and between-country variability in the availability of and access to PrEP within a spectrum of low- to high-income countries and even in those with early and successful PrEP roll-outs, including several EU countries.

A study from France published two years after PrEP approval reported that among PrEP non-users, 35%, 80%, and 37% were eligible to take PrEP, were aware of PrEP, and had the intention to take PrEP, respectively (27). The overlap of these three populations represented only 15% of non-user respondents. These results suggest that despite early approval of and free access to PrEP in France, barriers still

remain for PrEP uptake among men who have sex with men (MSM), resulting in lower-than-anticipated uptake of PrEP.

PrEP roll-out in Central and Eastern Europe (CEE) was much slower than in Western Europe (WE). In a previous study on PrEP (28), including 23 countries from the region, the majority of the respondents defined MSM with high-risk behaviors as the major target group for PrEP, whereas the percentage dropped significantly for heterosexuals and people who inject drugs (PWID). More than 70% of respondents reported being aware of "informal" PrEP use in their countries and almost 75% reported they would advise its use in their practice if they had access to it. This study showed that CEE countries were ready to accept and implement PrEP but only 34.2% of the respondents reported that PrEP was licensed in their countries. Türkiye was among the countries with no PrEP availability. A Hornet survey including more than 4700 respondents from Türkiye reported that approximately 40% of respondents were aware of PrEP, 2.5% had used PrEP in the previous year, and 1.7% were current users, primarily through the internet and pharmacies, which was off label use (29). Respondents younger than 25 years who are considered most at risk, were significantly less aware of and less willing to use PrEP compared to older respondents.

Up to date much has been accomplished in the region in terms of PrEP roll-out. A study in 2018 comparing the previous year in the same region reported a significant increase in the number of countries where PrEP was licensed (30). A more recent study comparing countries that responded to both surveys in 2018 and 2020 showed that the number was still on the rise in terms of PrEP licensing (68.4% vs. 75%), PrEP recommendation in guidelines (50% vs. 55%), and PrEP prescription free of charge (10.5% vs. 25%). However, informal PrEP use was also increasing (68.4% vs. 75%) (31).

Pre-exposure prophylaxis recently became available in Türkiye in November 2021. It was licensed as a generic formulation only in on-demand form. PrEP guidelines were produced and published in June 2022 (32). The first PrEP clinic was opened in November 2022 in the Ege University School of Medicine Department of Infectious Diseases and Clinical Microbiology.

In the CEE region, PrEP availability differs from country to country, either as daily or on-demand or both forms, and several countries have only one form available. There are wide disparities between countries in access to PrEP, ranging from <1% to 80%. Currently, around 80 centers in the region are offering PrEP (with almost a 1.5-fold increase compared to 2018) with an estimated number of 9000 people on PrEP, with a 2-fold increase compared to 2018 (31).

The major barriers to PrEP use were reported as lack of knowledge of people in need (58.3%), not being reimbursed (54.2%), low perception of HIV (45.8%), lack of knowledge of healthcare providers (14.7%), and fear of stigma and discrimination (33.3%) (31).

A study by ECDC including more than 100,000 respondents from 44 countries in Europe and Central Asia analyzed the PrEP gap, which was defined as the proportion of HIV-negative MSM who are 'very likely' to use PrEP if accessible, compared with the proportion currently using PrEP. While the overall PrEP gap was around 17%, it varied from 4% to 45%, with a much larger gap in non-EU and lower-income countries, several of which have large epidemics and rapidly rising new infections (33). There are also inequalities in PrEP access among key populations. Black MSM and women (34-36), ethnic minorities (36, 37), migrants (36, 37), young people (38, 39), and people who inject drugs (PWID) (40) who are in greater need have much lower access to PrEP than others.

COVID-19 also had a significant negative impact on prevention services in Europe. In a Hornet survey including more than 10,000 MSM across 20 countries, 56% of the respondents, including those from European countries, reported interruptions to PrEP. In addition, respondents from European countries reported lower perceived access to PrEP compared to other parts of the world, and greater proportions reported perceived interruptions in Mexico and Türkiye compared with other countries (41).

We are entering a new era in prevention. New tools have already arrived or are on the way in the near future. Tenofovir alafenamide (TAF) has received FDA approval recently (42); trials are running for lenacapavir (43); long-acting injectable cabotegravir has been approved by FDA, and several trials are still ongoing (44); dapivirine ring recently got approval for use in African women (45); and there are also ongoing vaccine and antibody studies (46). This field is open to development, and much has already been achieved.

Despite these achievements, the European region still lacks uniformity and we can summarize the current situation with a simple continuum. On one end of the continuum, there are countries with no or limited PrEP availability, no promotion for PrEP with no or limited use and a growing epidemic. Most non-EU CEE countries fall into this category. On the other end, there are countries in WE with a number of options for PrEP, extensive promotion, and widespread usage with significant decreases in new infections.

The European region still faces many challenges in terms of PrEP availability and usage. Current PrEP targets and PrEP availability differ across regions, countries, and settings due to significant variations in sociocultural and political structures and resources available. Most at-risk populations in greater need of prevention services have much lower access to PrEP, creating a major barrier to progress. The 3 million target set by UNAIDS covers only 10% of people at risk that could benefit from PrEP. (37). Annual PrEP initiations have gradually reduced over time from 97% in 2017-2018 to 55% in 2019-2020 (19). PrEP requires close monitoring, including regular HIV testing and STI screening. While this creates a great opportunity to improve STI control (47), it may also result in PrEP fatigue among healthcare providers due to increasing demand and lack of human and other resources.

Türkiye has taken a huge step forward by approving the registration of the on-demand PrEP formulation in the country and providing a specific guideline for PrEP. However, this is also an important limitation in that on-demand PrEP covers a very small portion of the population in need of PrEP, leaving outside women and those who are engaged in more frequent sex and require daily use.

Further steps to be taken by the Turkish government for a more effective PrEP roll-out are:

- Endorsement of the PrEP roll-out process and joint work in collaboration with physicians and civil societies;
- Approval of daily PrEP use in the country with no further delay;
- Full reimbursement of PrEP;
- Establishment of PrEP clinics in major cities with a large HIV population;
- Public awareness activities.

In conclusion, there has been great progress in PrEP availability in the European region recently. However, PrEP uptake globally and regionally still lacks the power to have an impact on controlling the epidemic. There is still much more to accomplish in terms of access or free access to PrEP. Socioeconomic, political, and cultural variations between countries have a significant impact on policies and need to be considered. Sharing expertise between countries and support from international organizations are required to overcome barriers and move forward quickly. High prioritization of PrEP targets will offer us a realistic chance of reaching the UNAIDS goal of a 90% reduction in HIV infections by 2030.

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