MODULE 9

STRATEGIC PLANNING

# WHO IMPLEMENTATION TOOL FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) OF HIV INFECTION

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World Health Organization

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# Introduction

Following the WHO recommendation in September 2015 that "oral pre-exposure prophylaxis (PrEP) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches", partners in countries expressed the need for practical advice on how to consider the introduction of PrEP and start implementation. In response, WHO has developed this series of modules to support the implementation of PrEP among a range of populations in different settings.

Although there is growing acknowledgement of PrEP's potential as an additional HIV prevention option and countries are beginning to consider how PrEP might be most effectively implemented, there has been limited experience with providing PrEP outside research and demonstration projects in low- and middle-income countries. Consequently, there is often uncertainty around many implementation issues. The modules in this tool provide initial suggestions for the introduction and implementation of PrEP based on currently available evidence and experience. However, it is recognized that this evidence may evolve following wider PrEP use; therefore, it is likely that this tool will require regular updating.

PrEP should not replace or compete with effective and well-established HIV prevention interventions, such as comprehensive condom programming for sex workers and men who have sex with men and harm reduction for people who inject drugs. Many people who could benefit most from PrEP belong to key population groups that may face legal and social barriers to accessing health services. This needs to be considered when developing PrEP services. Although the public health approach underpins the WHO guidance on PrEP, the decision to use PrEP should always be made by the individual concerned.

## Target audience and scope of tool

This PrEP tool contains modules for a range of stakeholders to support them in the consideration, planning, introduction and implementation of oral PrEP. The modules can be used on their own or in combination. In addition, there is a module for individuals interested in or already taking PrEP. (See Summary of modules below.)

This tool is the product of collaboration between many experts, community organizations and networks, implementers, researchers and partners from all regions. The information presented is aligned with WHO's 2016 consolidated guidelines on the use of antiretroviral drugs for HIV treatment and prevention.

All modules make reference to the evidence-based 2015 WHO recommendation on PrEP. They do not make any new recommendations on PrEP, focusing instead on suggested implementation approaches.

## Guiding principles

It is important to adopt a public health, human rights and people-centred approach when offering PrEP to those at substantial risk of HIV. Similar to other HIV prevention and treatment interventions, a human rights-based approach gives priority to issues concerning universal health coverage, gender equality and health-related rights including accessibility, availability, acceptability and quality of PrEP services.

## SUMMARY OF MODULES

**Module 1: Clinical.** This module is for clinicians, including physicians, nurses and clinical officers. It gives an overview of how to provide PrEP safely and effectively, including: screening for substantial risk of HIV; testing for HIV before initiating someone on PrEP and how to follow up PrEP users and offer counselling on adherence.

**Module 2: Community educators and advocates.** Community educators and advocates are needed to increase awareness about PrEP in their communities. This module provides information on PrEP that should be considered in community-led activities that aim to increase knowledge about PrEP and generate demand and access.

**Module 3: Counsellors.** This module is for staff who counsel people as they consider PrEP or start taking PrEP and support them in coping with side-effects and adherence strategies. Those who counsel PrEP users may be lay, peer or professional counsellors and healthcare workers, including nurses, clinical officers and doctors.

**Module 4: Leaders.** This module aims to inform and update leaders and decision-makers about PrEP. It provides information on the benefits and limitations of PrEP so that they can consider how PrEP could be effectively implemented in their own settings. It also contains a series of frequently asked questions about PrEP.

**Module 5: Monitoring and evaluation.** This module is for people responsible for monitoring PrEP programmes at the national and site levels. It provides information on how to monitor PrEP for safety and effectiveness, suggesting core and additional indicators for site-level, national and global reporting.

**Module 6: Pharmacists.** This module is for pharmacists and people working in pharmacies. It provides information on the medicines used in PrEP, including on storage conditions. It gives suggestions for how pharmacists and pharmacy staff can monitor PrEP adherence and support PrEP users to take their medication regularly.

**Module 7: Regulatory officials.** This module is for national authorities in charge of authorizing the manufacturing, importation, marketing and/or control of antiretroviral medicines used for HIV prevention. It provides information on the safety and efficacy of PrEP medicines.

**Module 8: Site planning.** This module is for people involved in organizing PrEP services at specific sites. It outlines the steps to be taken in planning a PrEP service and gives suggestions for personnel, infrastructure and commodities that could be considered when implementing PrEP.

**Module 9: Strategic planning.** As WHO recommends offering PrEP to people at substantial HIV risk, this module offers public health guidance for policy-makers on how to prioritize services, in order to reach those who could benefit most from PrEP, and in which settings PrEP services could be most cost-effective.

**Module 10: Testing providers.** This module is for people who provide testing services at PrEP sites and laboratories. It offers guidance in selecting testing services, including screening of individuals before PrEP is initiated and monitoring while they are taking PrEP. Information is provided on HIV testing, creatinine, HBV and HCV, pregnancy and STIs.



**Module 11: PrEP users.** This module provides information for people who are interested in taking PrEP to reduce their risk of acquiring HIV and people who are already taking PrEP – to support them in their choice and use of PrEP. This module gives ideas for countries and organizations implementing PrEP to help them develop their own tools.

**Module 12: Adolescents and young adults.** This module is for people who are interested in providing PrEP services to older adolescents and young adults who are at substantial risk for HIV. It provides information on: factors that influence HIV susceptibility among young people; clinical considerations for safety and continuation on PrEP; ways to improve access and service utilization; and inclusive monitoring approaches to improve the recording and reporting of data on young people.

## ANNEXES

**Review of evidence.** A wide range of evidence including the following two systematic reviews informed the 2015 WHO recommendation on PrEP for people at substantial risk of HIV infection: (i) Fonner VA et al. *Oral tenofovir-based HIV pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis of effectiveness, safety, behavioural and reproductive health outcomes*; (ii) Koechlin FM et al. *Values and preferences on the use of oral pre-exposure prophylaxis (PrEP) for HIV prevention among multiple populations: a systematic review of the literature*.

**Annotated Internet resources.** This list highlights some of the web-based resources on PrEP currently available together with the stakeholder groups they are catering to. WHO will continue to provide updates on new resources.

# The strategic planning module

When a country decides to include PrEP in its national HIV programme, a range of implementation issues have to be considered, such as cost-effectiveness, safety, and epidemiological impact. This strategic planning module is for public health officials and policymakers responsible for deciding to whom to offer PrEP for HIV prevention as a priority, where PrEP services could be provided, and how PrEP could be integrated into other health services *(1)*. In this module, strategic decision-making practices are described on how to identify people at substantial risk of HIV who could benefit from being offered PrEP.

**WHO Recommendation for PrEP**

The World Health Organization recommends that oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches *(strong recommendation; high-quality evidence)*.

## Defining "substantial HIV risk"

**Substantial risk of HIV infection** is defined as an incidence of HIV infection typically considered to be higher than three per 100 person-years in the absence of PrEP *(2)*. By offering PrEP to people at substantial risk of HIV, the greatest epidemiological impact and value for money can be obtained, although PrEP may be cost-effective at lower incidence rates in some settings *(3)*.

A number of different factors can influence whether people are at substantial risk for HIV, the most important of which are their own and their partner(s)' sexual and drug using behaviour and HIV status, and the overall background HIV prevalence and incidence where they live. People considered to be at substantial risk of HIV reside in most countries *(4)*, in particular:

- men who have sex with men
- people who inject drugs
- transgender women, and
- sex workers in many countries of sub-Saharan Africa

Specific population groups in southern and eastern Africa at substantial risk of acquiring HIV include:

- adolescent girls and young women
- people with concurrent or a high number of sexual partners
- people who have another sexually transmitted infection (STI), and
- serodiscordant couples, where evidence shows that the HIV-negative partner can benefit from taking PrEP when the partner with HIV is not virally suppressed on antiretroviral therapy (ART).

However, not all people within these groups may be at substantial risk for HIV acquisition, and identifying these groups and individuals can be challenging.

## Prioritizing PrEP for those at substantial risk of HIV

Reducing HIV transmission among groups with high HIV incidence is a priority for public health programmes. Epidemiological research conducted through national surveys, clinical trials and cohort studies has shown that HIV incidence varies considerably between and within different population groups. In order to make the most efficient use of resources, it is particularly important that more costly interventions such as PrEP are focused in geographical areas with

high HIV incidence (and prevalence), and within key and vulnerable subpopulations, as well as among people at substantial individual risk (regardless of geography or population group). The populations at risk, health system capacity, and available resources for HIV prevention will determine where and to which groups PrEP should be offered; in low-resource settings other HIV prevention interventions may prove more cost-effective *(5)*. Nevertheless, in most settings, PrEP will likely be cost-effective for people identified at substantial risk of HIV *(3, 6)*.

PrEP can still be considered in settings where HIV incidence and prevalence data are lacking. In those instances, local level data from a range of sources such as HIV testing services may allow for making estimates of HIV prevalence in order to identify people at high risk for HIV, although these sources have limitations. Strategic approaches that can be used to identify groups at higher risk of acquiring HIV are discussed in detail in this module.

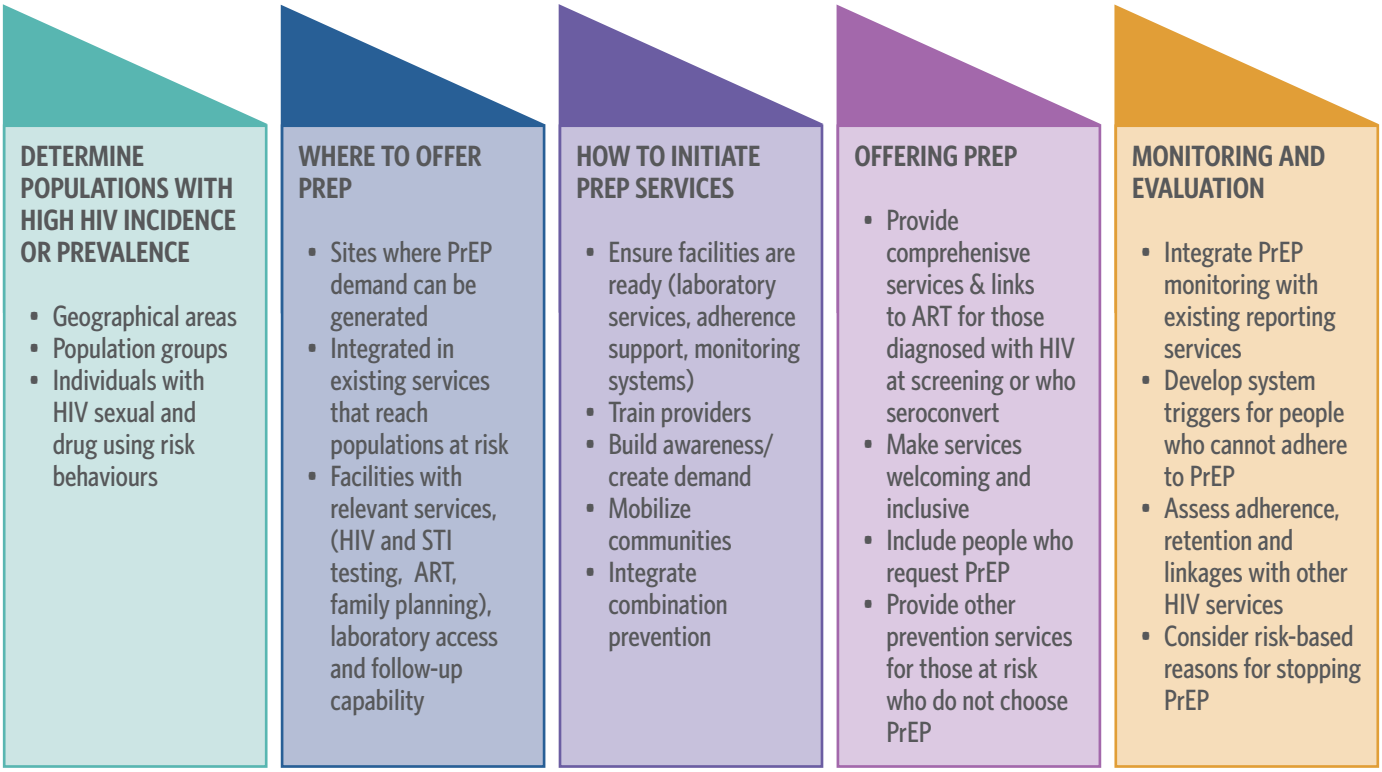
## Process for identifying people at substantial risk of HIV

From a strategic planning perspective, a multistage process could be helpful in identifying people at substantial risk of HIV, who could benefit from being offered PrEP as a priority (see Fig. 1). Firstly, a national HIV programme or public health jurisdiction will need to review the most recent epidemiological data on HIV at a national, regional and municipal level. This review would include data from specific populations, in order to identify groups where there is a high HIV incidence or prevalence and where it may be beneficial to offer PrEP services. Depending on the setting, these populations may be identified by a combination of geographical location, sex, age, or key population group.

Secondly, within populations and locations with higher HIV incidence or prevalence, a process for differentiating individuals at substantial risk of HIV from those who are not, can be considered. Individual need for PrEP could be assessed by: (1) using a risk calculator/score (see supplementary information A1-3), (2) assessing sexual and drug using behaviour, (3) considering persons who recognize their own HIV risk and request PrEP. Risk calculators have been developed and validated for different population groups, for example, men who have sex with men in the United States and Spain, and pregnant women and heterosexual serodiscordant couples in eastern Africa (see Supplementary information for examples). Clinicians may use a brief sexual and drug using history (as described in the clinical module of this PrEP implementation tool) to assess individual risk. In many situations, people who proactively ask for PrEP will already consider themselves to be at risk, and may have determined that PrEP is an appropriate prevention option. As such, they may be motivated to take PrEP and adhere to their regimen. In general, providers should consider offering PrEP to people who request it because, although these persons may recognize their own risk, they may not be able or willing to discuss this risk – either due to stigma or a reticence to talk to providers about sexual and drug using behaviour.

Thirdly, consideration should be given to where PrEP services could be established, including assessing the existing capacity and infrastructure of a given health jurisdiction (whether municipal, state or national) and factors that enable or inhibit access to, and provision of, services. Demand creation for PrEP may be necessary. It will usually not be appropriate to develop a standalone service for providing PrEP; rather, PrEP should be integrated into existing services, such as HIV testing, treatment and related services provided to key populations (for example, men who have sex with men, people who inject drugs, transgender people or sex workers). Sites that offer PrEP should cater and be easily accessible to populations that may benefit from PrEP. For example, in areas where there is a high HIV incidence or prevalence among young women, PrEP services could be integrated into facilities that are conveniently located and accessible for adolescent girls and young women, demonstrate cultural sensitivity towards women, and offer additional services, such as contraception and reproductive health services. Health services associated with tertiary education establishments could also be considered for integration of PrEP.

## FIGURE 1. STEPS IN PRIORITIZING AND IMPLEMENTING PREP SERVICES




## Observed HIV incidence rates among groups known to be at substantial risk

HIV incidence greater than three per 100 person-years has been observed among groups of men who have sex with men, transgender women, people who inject drugs, heterosexual men and women who have sexual partners with untreated HIV infection in all regions, sex workers in some settings in sub-Saharan Africa, and sexually active women and men in very specific geographical areas in southern and eastern Africa. Individual risk varies within these groups depending on individual behaviour and the characteristics of sexual partners.

Most PrEP trials have identified and recruited individuals from groups at substantial risk of acquiring HIV, as demonstrated by the high HIV incidence rates among participants in the control (non-PrEP) arms, which ranged from two to 8.9 per 100 person-years in almost all studies (see Table 1). HIV incidence in the control arms of PrEP trials was often higher than anticipated, suggesting that people drawn to participate in PrEP studies were at particularly high risk. For example, population surveillance estimated that HIV incidence would be three per 100 person-years among men who have sex with men in Paris and London; yet, PrEP trials in those cities (the Ipergay and PROUD studies) attracted men who have sex with men with an incidence of 6.6 and 8.9 per 100 person-years, respectively. Current experience suggests that PrEP uptake is strongly correlated with both perceived and actual HIV risk among men who have sex with men *(7, 8)*. Therefore, spreading awareness about PrEP and building demand might encourage those at risk to seek services. However, in a broader programmatic roll-out of PrEP, HIV incidence among people who choose to use PrEP may not be as high.

Table 1 demonstrates that the HIV incidence reported in the control (non-PrEP) arms of randomized controlled trials on PrEP was above two per 100 person-years for all population groups with the exception of people who inject drugs in the Bangkok Tenofovir Study (BKK TDF).

## TABLE 1. DIRECTLY MEASURED HIV INCIDENCE IN CONTROL (NON-PREP) ARMS OF PREP TRIALS

| STUDY | POPULATION | INCIDENT HIV INFECTIONS | PERSON-YEARS | HIV INCIDENCE RATE | 95% CI |
|---|---|---|---|---|---|
| BKK TDF *(9)* | PWID | 33 | 4823 | 0.7 | 0.47–0.96 |
| FEM PREP *(10)* | Women | 35 | n/a | 5.0 | n/a |
| VOICE *(11)* | Women | 60 | 1308 | 4.6 | 3.5–5.9 |
| iPrEx *(12)* | MSM and TGW | 83 | 2113 | 3.9 | 3.1–4.8 |
| iPrEx Gap *(12)* | MSM and TGW | 43 | 1044 | 4.1 | 3.1–5.6 |
| iPrEx OLE *(7)* | MSM and TGW | 13 | n/a | 2.1 | n/a |
| Partners PrEP *(13)* | Men and women in SDC | 52 | 1578 | 2.0 | 1.5–4.5 |
| TDF2 *(14)* | Men and women | 24 | n/a | 3.1 | n/a |
| PROUD *(15)* | MSM | 19 | 214 | 8.9 | n/a |
| Ipergay *(16)* | MSM | 14 | n/a | 6.6 | 6.0–12.7 |

Key: PWID: people who inject drugs; MSM: men who have sex with men; TGW: transgender women; SDC: serodiscordant couple.

# Epidemiological approaches to measuring HIV incidence

HIV incidence can be measured directly through epidemiological studies or indirectly through modelling. Directly measured HIV incidence is ideally determined through prospective cohort studies or serial surveys among a given population. Algorithms are another option, such as the Recent Infection Testing Algorithm that uses a number of laboratory tests, for example the limiting antigen avidity assay (LAg), to distinguish recent and established HIV infection *(17)*. Data from repeat testers can also be utilized.

However, directly measuring incidence is not always possible due to the expense and effort required. Other options include making inferences from HIV prevalence data and HIV programme data, such as HIV case reporting, and using mathematical models to estimate incidence within specific parameters *(18)*.

Using risk scores or risk calculators can also identify individuals at substantial HIV risk within a programme delivery setting and may be used to help persons considering PrEP to make an informed choice about starting PrEP.

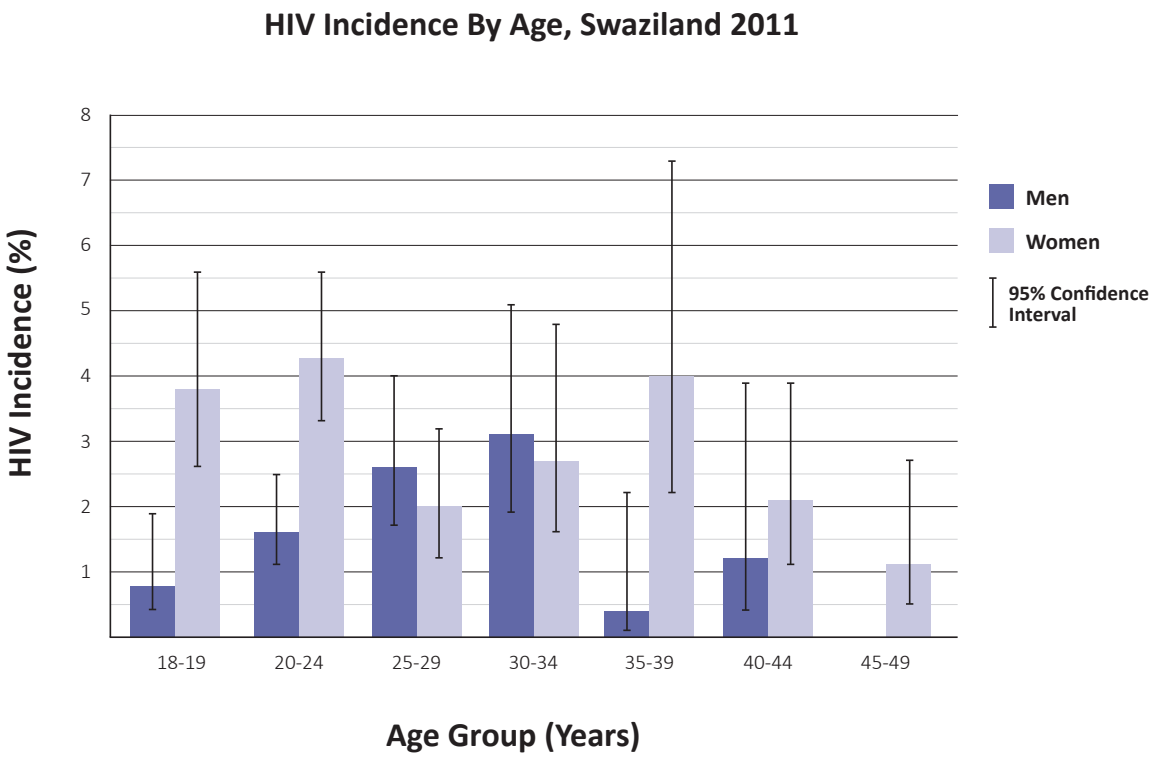
## Direct measures of HIV incidence

### a) Cohort studies and serial surveys

Population-based estimates of HIV incidence can come from serial surveys of a population or prospective cohort studies that follow people without HIV infection over time and determine the number of new infections that occur. These studies are ambitious, requiring time and resources, but provide a wealth of information including the prevalence and incidence of HIV among a number of different population groups. They can be small and continue for many years such as the Rakai Community Cohort Study in Uganda, or large serial surveys such as the nationally-representative Swaziland HIV Incidence Measurement Survey (SHIMS), which involved more than 18 000 households selected at random and tested for HIV in two cycles *(19, 20)*.

In settings with serial surveys or high quality cohort studies, using the data provided is a straightforward way to identify subpopulations at substantial risk of acquiring HIV who could benefit from being offered PrEP. The SHIMS serial survey showed that HIV incidence varies by age, geography and behaviour. For example, HIV incidence showed a bimodal distribution among women, where young women aged 18–24 years had an incidence of approximately four per 100 person-years and a second peak at ages 35–39 years (see Figure 2).

## FIGURE 2. HIV INCIDENCE IN SWAZILAND BY AGE AND SEX IN 2011




Source: Reprinted with permission from Elsevier (The Lancet, 2016, Feb;4(2):e83-e92).

Life events that have been associated with HIV risk include sexual violence, immigration to a region having a high prevalence of HIV, leaving school before completing educational goals and expulsion from home. Data from the same SHIMS study showed that the overall HIV incidence was 1.7% among men and 3.1% among women *(19).* Yet men who had more than two sexual partners in the preceding six months had an incidence of 3.2 per 100 person-years; while the incidence among women with similar sexual behaviour was 9.6 per 100 person-years (see Table 2). Therefore, even in a setting with very high HIV incidence, a phased implementation of PrEP could start by prioritizing those at highest risk.

## TABLE 2. NUMBERS OF SEX PARTNERS AND HIV INCIDENCE IN MEN AND WOMEN IN SWAZILAND

| SEX PARTNERS - PRECEDING 6 MONTHS | MEN HIV INCIDENCE | MEN HIV INCIDENCE 95% CI | WOMEN HIV INCIDENCE | WOMEN HIV INCIDENCE 95% CI |
|---|---|---|---|---|
| Never had sex | 0.15 | 0.03–0.83 | 0.71 | 0.22–2.26 |
| 0 | 0.40 | 0.08–2.05 | 1.21 | 0.61–2.38 |
| 1 | 1.92 | 1.40–2.64 | 3.64 | 3.01–4.41 |
| ≥2 | 3.21 | 2.02–5.10 | 9.64 | 4.48–20.0 |

Source: Swaziland HIV Incidence Measurement Survey *(19).*

### b) Repeat HIV testers

A further opportunity to measure HIV incidence in a population is by considering people who repeatedly test for HIV within a specific facility or programme. This is a self-selected sample and may provide inaccurate data if people who test often engage more or less frequently in risk behaviour compared with people who do not test often. In Barcelona, a community-based HIV testing clinic tracked men who have sex with men who tested more than once *(21)*. They found an incidence over three per 100 person-years among men who have sex with men who reported receptive anal intercourse with more than 10 sex partners, regardless of whether condoms were used or if STIs had been recently diagnosed (see Table 3). As with the iPrEx analysis among men who have sex with men and transgender women *(22)*, the majority of HIV infections among men who have sex with men in the Barcelona cohort study could be effectively prevented by offering PrEP.

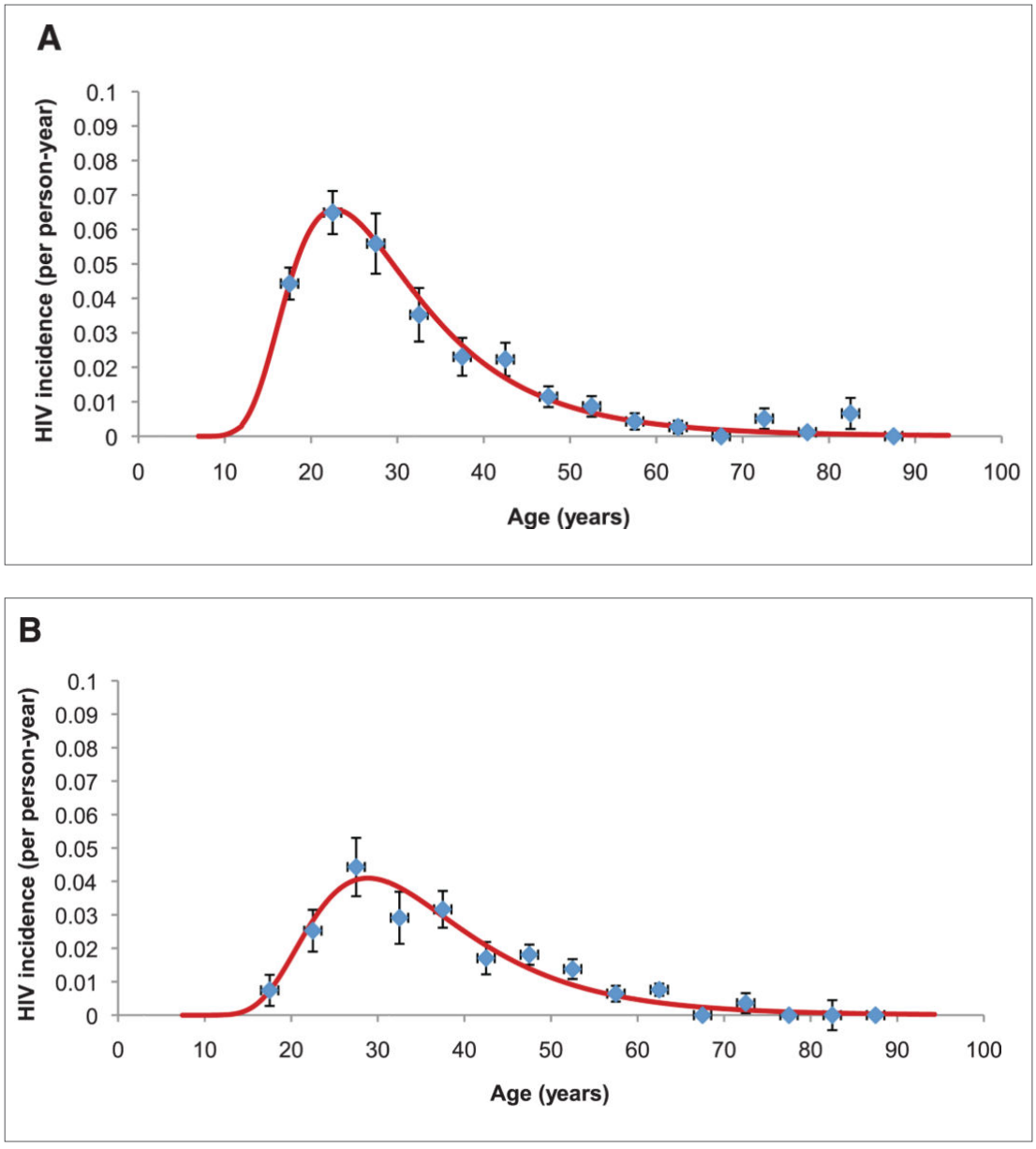
## TABLE 3. HIV INCIDENCE RATES IN A COHORT STUDY AMONG MEN WHO HAVE SEX WITH MEN IN BARCELONA

| HIV INCIDENCE GROUPS | | | | INDIVIDUALS INCLUDED | PERSON-YEARS | SERO-CONVERSION | INCIDENCE RATE | LOWER 95%CI | UPPER 95%CI |
|---|---|---|---|---|---|---|---|---|---|
| POSITION | CONDOM USE | STI | PARTNERS | | | | | | |
| ONLY INSERTIVE | USUALLY | NO STI | >10 | 250 | 635.3 | 6 | 0.9 | 0.4 | 2.1 |
| | | | >20 | 112 | 283.4 | 4 | 1.4 | 0.5 | 3.8 |
| | | STI | >10 | 14 | 41.6 | 2 | 4.8 | 1.2 | 19.2 |
| | | | >20 | 10 | 25.7 | 2 | 7.8 | 2.0 | 31.1 |
| | SOMETIMES | NO STI | >10 | 36 | 91.9 | 5 | 5.4 | 2.3 | 13.1 |
| | | | >20 | 27 | 55.5 | 5 | 9.0 | 3.8 | 21.6 |
| | | STI | >10 | 6 | 11.9 | 1 | 8.4 | 1.2 | 59.9 |
| | | | >20 | 5 | 6.3 | 1 | 15.8 | 2.2 | 111.9 |
| ANY RECEPTIVE | USUALLY | NO STI | >10 | 328 | 731.4 | 29 | 4.0 | 2.8 | 5.7 |
| | | | >20 | 164 | 370.7 | 19 | 5.1 | 3.3 | 8.0 |
| | | STI | >10 | 26 | 64.4 | 3 | 4.7 | 1.5 | 14.4 |
| | | | >20 | 16 | 41.8 | 2 | 4.8 | 1.2 | 19.2 |
| | SOMETIMES | NO STI | >10 | 71 | 166.6 | 15 | 9.0 | 5.4 | 14.9 |
| | | | >20 | 43 | 88.3 | 10 | 11.3 | 6.1 | 21,1 |
| | | STI | >10 | 8 | 16.2 | 4 | 24.7 | 9.3 | 65,8 |
| | | | >20 | 6 | 13.3 | 3 | 22.6 | 7.3 | 70.0 |

Source: Meulbroek M et al. *(21).*

Data from repeat testers in the South African province of Kwazulu-Natal also estimated incidence to be higher than three per 100 person-years among women aged 16–36 (see Figure 3/A) and men aged 22–38 (see Figure 3/B) *(23).*

## FIGURE 3. FEMALE (A) AND MALE (B) AGE VARIATIONS IN HIV INCIDENCE (95% CI) AMONG REPEAT TESTERS IN KWAZULU-NATAL, SOUTH AFRICA




Source: Tanser et al., SCIENCE 339:966 (2013). Reprinted with permission from AAAS.

### c) Laboratory assays

Laboratory assays, such as the LAg assay, measure recent HIV infections *(24).* When these assays are done on blood samples from survey participants they can provide information on HIV incidence among the populations the participants represent. Although assays can be indicators of recent infection, misclassifications are possible and challenges exist with some HIV-subtypes such as subtype F. For further information, see the WHO/UNAIDS *Technical update on HIV incidence assays for surveillance and epidemic monitoring (25).*

## Indirect measures of HIV incidence

### a. HIV prevalence as a proxy of HIV incidence

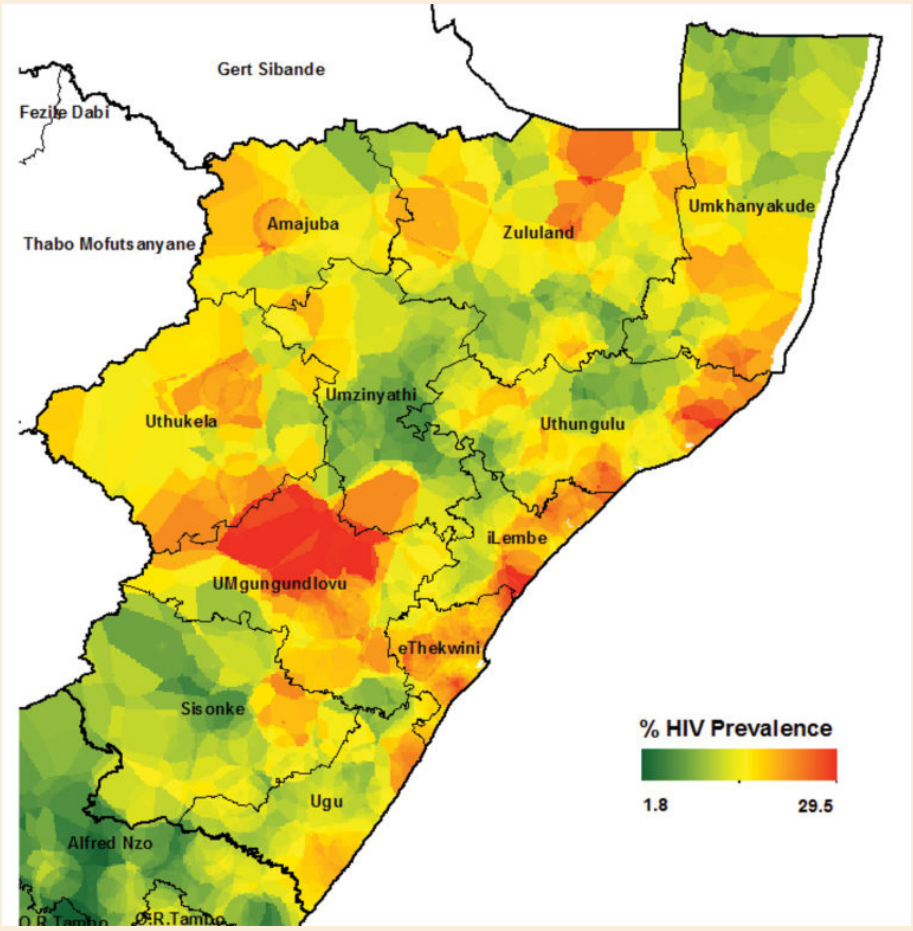
Direct measurements of HIV incidence are not often available for all populations and countries. There are substantial costs in undertaking serial surveys and longitudinal cohorts.

In the absence of direct measurements of HIV incidence, HIV prevalence may provide an indication of incidence, particularly if the data are recently collected or are for defined populations (such as key populations). Data on high HIV prevalence by age, sex, key population group or in relation to individuals demonstrating sexual behaviour associated with high HIV risk could provide an initial indication for decision-makers as they consider who would be prioritized for PrEP and where PrEP services could be offered.

Geographical mapping can provide a clear visualization of areas with high HIV prevalence. These areas may also have high numbers of new infections and therefore be places where providing PrEP services could be beneficial. Examples from South Africa and the United States are shown in Boxes 1 and 2, respectively. Relying on HIV prevalence alone, however, requires caution as prevalence does not always align with incidence. Populations in whom the highest proportion of new infections are occurring could be missed.

## Box 1. Identifying locations with high HIV prevalence/incidence that may benefit from PrEP services in Kwazulu-Natal

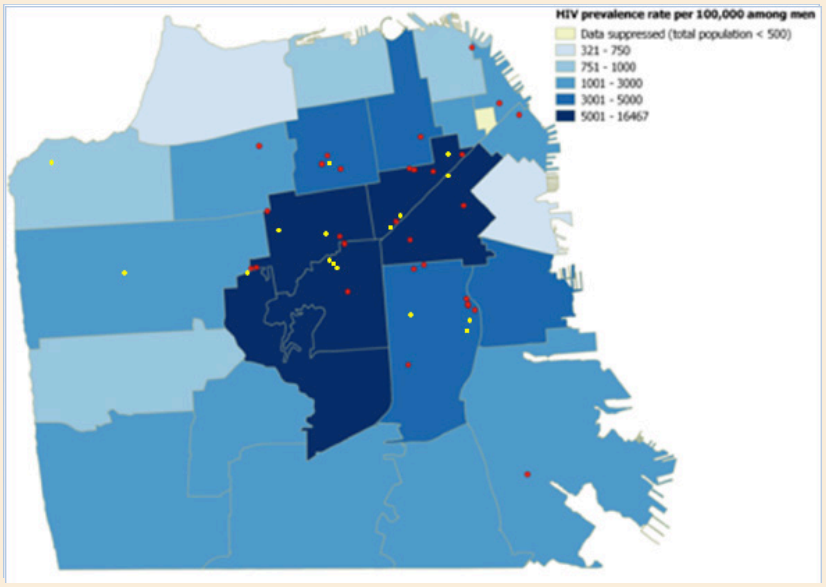
In the Kwazulu-Natal province of South Africa extensive surveillance data was used to identify areas with high HIV prevalence and incidence. The burden of HIV infection was seen to be accumulating rapidly among younger girls and adolescent women. Using HIV positivity from sites offering prevention of mother-to-child transmission services, a detailed geographical map of estimated HIV prevalence was created.




Source: Wanyeki I, Mitto B, Nganga L, Brodsky I, Datar A, Palmer E. HPP GeoHealt h Mapping: Using Geospatial Analysis to Understand the Local HIV Epidemic in KwaZulu-Natal Province and eThekwini Municipality in South Africa. Washington, DC: Futures Group, Health Policy Project; 2015.

## Box 2. Aligning PrEP services with HIV burden in San Francisco

HIV surveillance by the San Francisco Department of Public Health in 2015 provided characterization of newly diagnosed cases of HIV infection in San Francisco by demographic group and geographical location. A large burden of HIV infection is among men who have sex with men in the city. The number of people with HIV infection was mapped against the San Francisco city map (see below). The dots on the map indicate the locations of PrEP providers who were registered with the University of California, San Francisco online database as of 2015 (red dots) and June 2017 (yellow dots).




Source: San Francisco Department of Health and www.PleasePrEPme.org

### b. Mathematical models to estimate HIV incidence

Mathematical models are increasingly sophisticated and can now estimate HIV incidence at subnational levels. Country-specific data, assuming it is of sufficient quality, can be entered into models such as the Spectrum AIM model and used to estimate new infections over time by geographic region, age and sex. The goals component of the Spectrum model can be used to assess the epidemiological and economic impact and cost of implementing different programmes, including PrEP, on the trajectory of the HIV epidemic.

### c. Other methods

Programme data from HIV testing sites are another approximate means of estimating HIV prevalence in certain populations. These data have many limitations and should be avoided if possible. For example, many people do not utilize health facilities; therefore, the proportions who test HIV-positive in health facilities do not necessarily represent community HIV prevalence or incidence. Moreover, differences in the proportions testing, and testing HIV-positive, may depend on the type of testing facility. For example, antenatal clinics provide services to women in the general population and typically have high HIV test uptake, whereas standalone testing sites rely on people presenting themselves for testing based on their own risk perception. When assessing the proportions of people testing HIV-positive these factors should be taken into consideration and any extrapolation of data to estimate prevalence in populations outside the testing clinics made with caution. Bearing in mind these limitations, programme data from HIV testing sites could be used to estimate the number of people using services and the HIV prevalence among certain populations, such as pregnant women who access antenatal care. Programme data can also be used to adjust national or regional prevalence data from sero-surveys to estimate HIV prevalence at subnational levels. None of these approaches on their own will provide sufficient information for decision-making regarding which populations to offer PrEP to; however, they could be used to focus strategies for PrEP roll-out in geographical regions with high HIV prevalence. Also, behavioural data from individual risk assessments can be informative in offering PrEP to the most at risk individuals.

## Assessing individual risk for HIV infection

Ultimately, people who could be offered PrEP are those who are considered to be at substantial individual risk of HIV acquisition regardless of geographic residence or population group. Using HIV incidence, prevalence and modelling data to

understand which people are at substantial risk and where they reside is a first step for policy-makers when considering where to start offering PrEP services. The provision of PrEP to all persons at substantial risk will maximize its impact at a population level. However, not all members of an identified population will be at substantial risk, and others at substantial risk will be in non-priority populations and geographies.

A second step is to identify where persons at substantial risk most commonly access services. Health care workers need to be able to identify individuals at substantial HIV risk who may benefit from taking PrEP. The simplest means of doing this is through conversations between clinicians and clients as part of a consultation. Another approach is to use individual risk calculators. People may also self-identify as being at risk depending on their sexual or drug using behaviour, however, some people may not be willing to disclose this to health care workers.

Individuals testing HIV-positive should be offered assisted partner notification services for all their sexual and drug injecting partners, and if they are in a serodiscordant relationship PrEP could be considered for the HIV-negative partner until the HIV-positive partner achieves viral suppression.

### Individual risk calculators

Individual risk calculators assess a person's risk for HIV acquisition based on a number of simple questions that are totalled to reach a final risk score. The total scores can be categorized to provide a guide for thresholds at which to offer PrEP. Individual risk calculators were used in the Partners Demonstration Project of PrEP and ART in Kenya and Uganda, where risk scores were developed to identify serodiscordant couples at highest risk for HIV-1 transmission. PrEP was offered to the HIV-negative partner until the HIV-positive partner was virally suppressed on ART (see Supplementary information A.1). A score of five or more predicted an HIV incidence of 4.5 per 100 person-years and was used to identify higher risk couples *(26, 27).*

Another risk assessment tool that was used to identify pregnant and postpartum women who might benefit from PrEP was developed by a cohort study in Kenya (see Supplementary information A.3) *(28)*. An internally validated simplified risk score based on factors including whether the respondent knew her male partner's HIV status, her lifetime number of sexual partners and whether she had a laboratory-confirmed syphilis diagnosis found that women with simplified scores greater than six accounted for 16% of the population but 56% of HIV acquisitions. The authors concluded that a combination of indicators routinely assessed in antenatal clinics predict HIV risk and could be used to prioritize which pregnant women to offer PrEP to. The U.S. Centers for Disease Control and Prevention (CDC) published a HIV risk index for men who have sex with men in the United States as part of their PrEP providers guidance (see Supplementary information A.2).

Risk calculators may need to be developed, adapted and evaluated for different settings since indicators of incidence will differ depending on HIV prevalence and the distribution of persons with untreated HIV infection. Therefore, risk calculators may not apply uniformly to all populations, and research is needed to determine the usefulness of risk scores in different populations before they are implemented. Risk calculators should be used with caution; some PrEP providers may not wish to use them or some PrEP users may not want to answer the related questions. Risk calculators should not be used to exclude people from PrEP services, especially if they present at facilities having self-identified as being at risk and are motivated to take PrEP.

## Identifying incidence thresholds for cost-saving PrEP implementation

Following an epidemiological analysis to determine regions and populations at risk and their approximate population sizes, governments and country programmes will need to determine the HIV incidence threshold for which providing PrEP would be cost-effective. HIV incidence thresholds for offering PrEP will vary depending on a variety of considerations, including epidemiological context, trends in HIV transmission, available resources and the relative costs, feasibility, and demand for PrEP. For example, the 2014 recommendation by the International Antiviral Society, an expert panel in the United States, considered an HIV incidence greater than two per 100 person–years to be sufficient to warrant offering oral PrEP *(29)*. This threshold was intended to achieve cost-effective PrEP implementation *(30, 31)*.

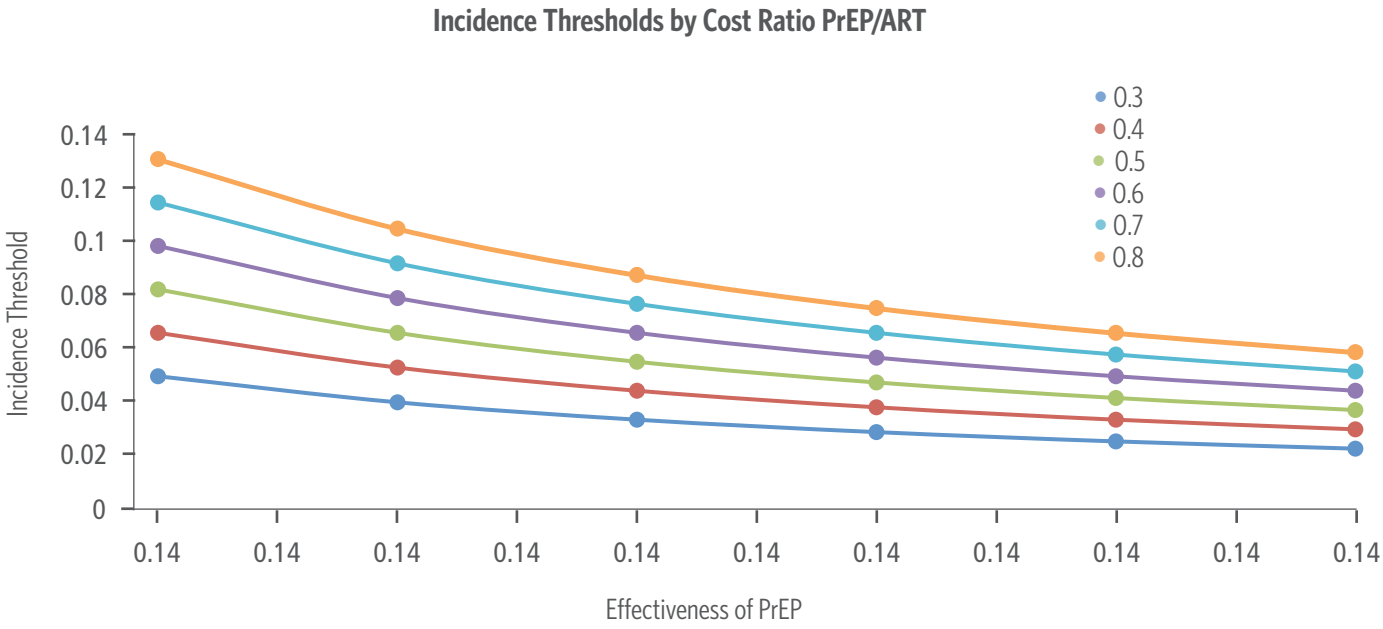
The HIV cost-effective incidence threshold developed by UNAIDS is defined as the background HIV incidence that saves more in treatment costs than the cost of providing PrEP (see Figure 4). This threshold depends upon the incidence of HIV in the absence of PrEP, PrEP effectiveness and the relative costs of providing PrEP (for example for one year) compared to the treatment costs for HIV infections that occur without the use of PrEP. Relative costs of PrEP and ART vary depending on antiretroviral medicine prices and the frequency of laboratory testing, HIV testing, viral load monitoring, and CD4 monitoring. HIV treatment is assumed to be lifelong with substantial discounting of future expenses. PrEP is likely to be cost-effective over the long term if provided to people at over 3% risk of HIV infection per year.

In general, PrEP is expected to cost approximately 40% of the cost of HIV treatment, although this can vary depending on the relative costs of medical services, medicines and laboratory tests in different settings. Delivery models in which there are fewer facility visits for adherent PrEP users, shorter duration of PrEP use, and where there is staff task sharing, may reduce costs.

In randomized controlled trials, the effectiveness of PrEP compared to a placebo varied from 0% to 86% *(32)*. These randomized controlled trial estimates may not apply to clinical practice, where PrEP users know they are taking active medicines and clearer information about PrEP safety and efficacy is provided. In some PrEP programmes, 80–90% of the retained population of PrEP users achieve effective concentrations of PrEP medicines *(8, 15, 33).* People who are not retained do not contribute to programme costs or impact.

Several circumstances would increase the incidence threshold for cost-effective PrEP implementation. For example, using viral nucleic acid testing routinely to rule out acute HIV infection or the need for more frequent visits for adolescent populations would increase implementation costs. Also, PrEP effectiveness and impact may be low if PrEP services are not well planned and delivered and if uptake and retention is poor, or if adherence to PrEP is low.

### FIGURE 4. MODELLED HIV INCIDENCE THRESHOLDS FOR COST-EFFECTIVE IMPLEMENTATION OF PREP BASED ON RELATIVE COSTS OF PREP AND HIV TREATMENT AND PREP EFFECTIVENESS




Source: UNAIDS

## Programming PrEP services

The provision of PrEP is relatively complex when compared with other biomedical HIV prevention tools. For example, condoms are cheap, relatively easily available and effective if used correctly, and are not associated with adverse events. Also, voluntary medical male circumcision provides approximately 60% lifetime protection for heterosexual men and is an inexpensive single event. In settings in sub-Saharan Africa with high or moderate HIV prevalence in the general population, voluntary medical male circumcision among adult men is a cost-effective HIV prevention strategy that reduces long term costs compared to treatment only strategies *(34)*. In contrast, PrEP is more expensive, requires high adherence among users and long-term client monitoring through laboratory tests and repeated HIV testing. On rare occasions, PrEP may cause serious adverse events. Thus, careful thought is needed to decide where and how to offer PrEP as part of combination prevention options in a given country and context.

In many settings, the most feasible way to consider implementing PrEP is to integrate PrEP within existing services, for example within services for key populations – such as men who have sex with men, sex workers, people who inject drugs and transgender people – or those that provide HIV testing, STI screening, condoms and other family planning services. Some locations that serve key populations may not have onsite laboratory facilities. In these cases, it may be feasible to

collect biological samples, such as blood samples for creatinine testing, and send them to external laboratories for testing as long as follow-up schedules are maintained for all persons initiating PrEP.

Sites such as antenatal or ART clinics that identify or have had serodiscordant couples referred to them can consider offering PrEP to the HIV-negative partner if the HIV-positive partner is not yet virally suppressed.

In countries with a high HIV incidence among adolescent girls and young women, PrEP services could be offered in facilities that provide family planning or other reproductive health services such as STI clinics or clinics providing services for women in tertiary education.

In very high HIV burden settings, women continue to acquire HIV during pregnancy and breastfeeding, which accounts for a significant proportion of infants with HIV. As antenatal services successfully test and provide treatment to all women with HIV as part of prevention of mother-to-child transmission programmes, mother-to-child transmission will continue to decline. To further reduce HIV transmission from mothers to infants and to complement existing HIV prevention strategies, PrEP could be offered as part of antenatal and postnatal services to women at substantial risk.

As awareness about the benefits of PrEP grows, people who consider themselves to be at substantial risk of HIV may self-select and seek to obtain PrEP from their regular healthcare provider. Ultimately, PrEP should be available as an additional choice to those who want and need it as part of a comprehensive combination HIV prevention package.

## Special considerations for offering PrEP to adolescents and young people

Older adolescents and young people at substantial risk of HIV could also be included in PrEP services. In most settings in sub-Saharan Africa, rates of HIV incidence are significantly higher in adolescent girls and young women than adolescent boys and young men. Young men who have sex with men and young transgender women may have substantial HIV risk in many settings in all regions. Therefore, it will usually be more appropriate to consider these groups of adolescents (rather than all adolescents) for PrEP services. It is important for providers to sensitively and non-judgementally engage in a discussion with young people about their sexual partners, possibly including transactional sex, and recognize and minimize risks of intimate partner violence while assessing HIV prevention options. Providers may encounter situations where the age of consent for HIV testing and receiving prescription medicines is a barrier to providing services. The provision of health services to adolescents in a safe environment without the involvement of law enforcement is important to enable adolescent girls, young men who have sex with men and transgender people, and young people who inject drugs to access HIV testing and ART if diagnosed HIV-positive or prevention services, including PrEP, if HIV-negative.

Concerns about potential HIV exposure may be more emotionally challenging for adolescents, particularly where partnership dynamics are unequal. The potential loss of social and economic support, or the loss of a partner, may be especially difficult for adolescents, particularly if the partner is older and/or has more power in the relationship. Adolescents whose behaviours are criminalized or stigmatized – such as those who engage in transactional sex, men who have sex with men, people who inject drugs and transgender people – may be even more vulnerable to exploitation and may have difficulty in accessing services. Providers should consider appropriate ways of engaging with adolescents to encourage them to access health facilities as well as support services should they be required.

Ensuring adherence to PrEP among adolescents may be more challenging than among adults due to developmental, legal, economic or social factors that may affect their ability to access services. Creating an enabling environment such as flexible hours and peer groups, with sensitization training for staff on how to provide youth-friendly and inclusive services at facilities offering PrEP, is a first step. Ensuring that the requirements for providing PrEP (such as repeat laboratory testing and regular follow-ups) are possible and understood by adolescents will also be important. Creative solutions may be required to enable adolescents to access services and successfully initiate PrEP. These may include mobile phone text message-based adherence support, varied clinic hours, or other youth-friendly technology-based services and outreach services.

More frequent follow-up of adolescents taking PrEP may be necessary. A trial among young men who have sex with men in the United States found that while PrEP acceptability was high, laboratory measured adherence dropped substantially when follow-up visits changed from monthly to quarterly *(35)*. Similar results were found in South Africa *(36).* Adherence to a topical PrEP formulation (gels and rings) in trials was much lower among young women under the age of 25, although the HIV incidence in that group was up to three-fold higher than women over 25 *(11, 37)*. In a programmatic setting, when young people either self-select for PrEP or are offered PrEP based on their risk, they may be highly motivated to initiate and adhere to PrEP in order to protect themselves. However, they may need repeated counselling to remain motivated.

# Supplementary information. Examples of risk calculators

## A.1. Heterosexual serodiscordant couples

A risk score for heterosexual serodiscordant couples was published and validated in the Partners Demonstration Project in Kenya and Uganda *(38).* A score over 3 predicted HIV incidence of greater than 3 per 100 person-years and a score of over 5 predicted HIV incidence greater than 4.5 per 100 person-years. A score of 5 was used to define the HIV-negative partner's eligibility to take PrEP. The score incorporated information about the viral load of the HIV-positive partner.

### TABLE A.1. HIV ACQUISITION RISK SCORE WORKSHEET FOR SERODISCORDANT COUPLES IN KENYA AND UGANDA

| RISK FACTOR | VALUE PER FACTOR | SCORE |
|---|---|---|
| **Age of HIV-1-uninfected partner** | | |
| 20 years or less | 4 | |
| 21-30 years | 1 | |
| More than 30 years | 0 | |
| **Number of children** | | |
| 0 | 2 | |
| 1-2 | 1 | |
| 3 or more | 0 | |
| **Male HIV-1-uninfected partner uncircumcised** | | |
| Yes | 1 | |
| No | 0 | |
| **Married and/or cohabiting** | | |
| Yes | 1 | |
| No | 0 | |
| **Unprotected sex within partnership, prior 30 days** | | |
| Yes | 2 | |
| No | 0 | |
| **HIV-1 plasma viral load, HIV-1-infected partner** | | |
| 50,000 copies or higher | 3 | |
| 10,000-49,999 copies | 1 | |
| Less than 10,000 copies | 0 | |
| **Total score** | | |

Source: Kahle EM et al, 2013. *(38)*

## A.2. Men who have sex with men

The CDC published a HIV risk index for men who have sex with men in the United States as part of their PrEP providers guidance *(39)*. This risk calculator may be adapted for use in other settings and with other populations, including heterosexual men and women, transgender men and women, and people who inject drugs.

More information is available here: https://www.cdc.gov/hiv/pdf/prepprovidersupplement2014.pdf

## TABLE A.2. CDC HIV RISK INDEX FOR MEN WHO HAVE SEX WITH MEN IN THE UNITED STATES

| MSM RISK INDEX | | |
|---|---|---|
| 1. How old are you today? | If <18 years, score 0 | |
| | If 18-28 years, score 8 | |
| | If 29-40 years, score 5 | |
| | If 41-48 years, score 2 | |
| | If 49 or more, score 0 | |
| 2. In the last 6 months, how many men have you had sex with? | If >10 male partners, score 7 | |
| | If 6-10 male partners, score 4 | |
| | If 0-5 male partners, score 0 | |
| 3. In the last 6 months, how many times did you receptive anal sex (you were the bottom) with a man without a condom? | If 1 or more times, score 10 | |
| | If 0 times, score 0 | |
| 4. In the last 6 months, how many of your male sex partners were HIV-positive? | If >1 positive partner, score 8 | |
| | If 1 positive partner, score 4 | |
| | If <1 positive partner, score 0 | |
| 5. In the last 6 months, how many times did you have insertive anal sex (you were the top) without a condom with a man who was HIV-positive? | If 5 or more times, score 6 | |
| | If 0 times, score 0 | |
| 6. In the last 6 months, have you used methamphetamines such as crystal or speed? | If yes, score 6 | |
| | If no, score 0 | |
| | Add down entries in right column to calculate total score | |
| | | TOTAL SCORE* |

* If score is 10 or greater, evaluate for intensive HIV prevention services including PrEP. If score is below 10, provide indicated standard HIV prevention services.

Source: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Providers' Supplement. United States Centers for Disease Control and Prevention, 2014.

## A.3. Pregnant and postpartum women

A risk score to identify pregnant and postpartum women who might benefit from PrEP was developed by a cohort study in Kenya *(28)*. Women with simplified scores greater than 6 accounted for 16% of the population but 56% of HIV acquisitions. The authors conclude that a combination of indicators routinely assessed in antenatal clinics predicted HIV risk and could be used to prioritize which pregnant women are offered PrEP.

### TABLE A.3. HIV RISK SCORE FOR PREGNANT AND POSTPARTUM WOMEN IN KENYA

| RISK FACTOR | VALUE PER FACTOR | COMPLETE SCORE | SIMPLIFIED SCORE |
|---|---|---|---|
| **No. of lifetime sexual partners** | | | |
| 1 point per sexual partner | Enter at least 1 | | |
| **Male partner HIV status** | | | |
| Known or no male partner | 0 | | |
| Unknown | 6 | | |
| **Syphilis** | | | |
| RPR nonreactive | 0 | | |
| RPR reactive | 5 | | |
| **Bacterial vaginosis** | | | |
| Negative or not screened | 0 | | |
| Positive | 2 | | |
| **Candidiasis** | | | |
| Negative or not screened | 0 | | |
| Positive | 3 | | |
| **Total risk score** | | | |

Source: Pintye et al, 2016. *(28)*

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