

Recommendations on the Use of PrEP for All Populations
PEPFAR Scientific Advisory Board (SAB)
Submitted by the PrEP Expert Working Group (EWG) to the SAB
Approved by the SAB on October 14, 2015

Members of the PrEP EWG

Dr. Quarraisha Abdool Karim, Co-chair
Dr. Jared Baeten
Dr. Connie Celum, Chair
Dr. Robert Grant
Dr. Nina Hasen
Dr. Colleen Kelley
Dr. Fabio Mesquita
Dr. Helen Rees
Dr. Heidi Van Rooyen
Mr. Mitchell Warren

Representatives from the Office of the U.S. Global AIDS Coordinator (S/GAC), Department of State

Dr. Maureen Goodenow
Dr. Julia MacKenzie
Dr. Douglas Shaffer

Broad Objectives of the PrEP EWG:

To formulate recommendations for the PEPFAR Scientific Advisory Board's consideration on the prioritization, support and logistics of implementing PEPFAR-funded pre-exposure prophylaxis (PrEP).

Process Overview:

These recommendations are based on four teleconferences and email correspondence that included members of the PrEP EWG and representatives from S/GAC. The PrEP EWG reviewed existing peer reviewed documents, unpublished reports and systematic reviews. Special thanks and acknowledgement to: Rachel Baggaley and Meg Doherty from the World Health Organization (WHO), as well as EWG members Bob Grant and Jared Baeten for access to documents that were not yet in the public domain. Thanks also to S/GAC representatives and secretariat support for access to documents related to drug access, and the PEPFAR DREAMS initiative.

Summary of PrEP Efficacy, Adherence and Implementation

PrEP with oral tenofovir (TDF) or TDF co-formulated with emtricitabine (TDF/FTC) demonstrated substantial HIV prevention benefits (up to 75% reduction in HIV incidence) in trials conducted among men who have sex with men (MSM); people who inject drugs (PWID) in Thailand; HIV serodiscordant couples in Kenya and Uganda; and young men and women in Botswana. Subgroup analyses estimated efficacy to be very high (range from 80-92%) among those who had tenofovir in their blood samples. PrEP efficacy among women was high (approximately 70% compared to placebo and ~90% when tenofovir was detected in blood) in the Partners PrEP Study, including among younger women. In contrast, in the oral PrEP efficacy trials (VOICE and FEM-PrEP) and daily and peri-coital tenofovir gel efficacy trials (VOICE and FACTS, respectively) among young

African women, efficacy was not demonstrated due to low levels of adherence to study product by study participants.

Qualitative research during and after the VOICE and FEM-PrEP trials identified a number of factors that influenced the low use of PrEP, many of which were specific to the context of placebo-controlled clinical trials. These factors included motivations to take part in trials for access to quality health services, monetary reimbursement for study visits, monthly reminders that they may be in a placebo arm and not receiving active product, and that the active product had not been determined to be effective. Gender and power dynamics, and poor perception of their HIV risk also undermined PrEP use and could be factors during implementation in clinical practice as well.

The overall body of evidence for TDF-based oral PrEP is that it is a proven intervention that persons can use during periods of HIV risk, such as related to having a partner of unknown HIV status, unprotected sex when trying to conceive, with casual partners or when in an early stage of a relationship, and when they are unable to negotiate or utilize condoms, in settings with high HIV incidence rates. For HIV serodiscordant couples, PrEP provides the couple a way to achieve safer conception and protection for the HIV-uninfected partner until the HIV-infected partner initiates ART and is virally-suppressed. PrEP is also an additional option for HIV prevention for young women, MSM, PWID and sex worker populations.

PrEP in the form of one pill a day is an intervention that can be used discreetly and independently and has the potential to significantly reduce HIV acquisition at an individual and population level. Open label studies undertaken to date either as demonstration projects, post-trial access or standard of care consistently highlight that if individuals, including young people, know that PrEP works, they are more likely to use it and be adherent. Moreover, these projects have found that uptake is higher in those who self-identify as at HIV risk.

Thus, with strong evidence for the efficacy and effectiveness of daily oral PrEP across multiple studies, it is a public health priority for PEPFAR to make PrEP available in high HIV prevalence settings in a strategic fashion to people at substantial risk, including adolescent girls and young women, HIV serodiscordant couples, female sex workers, men who have sex with men, and injection drug users, based on their risk.

In order not to duplicate already available information, the EWG drew on several key documents. Most important and critical was an extensive and comprehensive systematic review undertaken by WHO in preparation for the recently released WHO ARV guidelines, which provides compelling evidence for TDF-based PrEP provision for all populations at high risk (provisionally defined as having an incidence rate of $\geq 3/100$ p-y of follow-up on a population and geographic basis) of acquiring HIV and has been included in the recently released revised WHO ARV guidelines. WHO PrEP recommendations released on September 30, 2015 make a “Strong, High-quality” recommendation 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 prevention approaches”. WHO is planning to release implementation guidance providing more specific operational guidance early in 2016. This guidance based on best available data was also utilized to specifically guide recommendations on drug choices, safety monitoring, principles of adherence support, and use of PrEP during pregnancy outlined below.

Recommendations for Targeting PrEP within PEPFAR

1. Prioritize PrEP for young women geographically in the 10 PEPFAR DREAMS countries, for counties and provinces with high HIV prevalence and incidence

Over 50% of all new HIV infections taking place globally occur in the 10 PEPFAR countries prioritized for the DREAMS initiative. The high HIV incidence among young African women persists in spite of scale up of HIV testing, antiretroviral treatment as prevention and voluntary medical male circumcision. One of the core PEPFAR targets for 2017 is to reduce incident HIV infections in young women aged 15-24 years by 40% with an initial reduction of 25% in 2016 through the PEPFAR DREAMS initiative. A core strategy for reaching this target reduction in HIV incidence in DREAMS is PrEP included within the context of a broader combination prevention approach. The strengthening of efforts to engage men in HIV prevention efforts and encouraging men to know their HIV status and be initiated on ARV treatment if infected, or undergo VMMC (if virally suppressed or HIV uninfected) and use available prevention options consistently, will indirectly impact HIV risk reduction in young women.

- a) The PrEP EWG recommends prioritizing PrEP for young women (15-24 years), who contribute a disproportionate number (one third) of all new HIV infections in eastern and southern Africa, which is more than four times that of their male peers. HIV risk in young women is driven by social, behavioral and biological vulnerability, which amplify each other. Young women who are most likely to acquire infection are typically from socio-economically deprived households within high HIV prevalence communities, have limited or no schooling, engage in transactional sex or other high risk coping behaviors, and have histories of sexually transmitted infections and/or pregnancy.
- b) It is essential to offer young African women oral PrEP and support adherence in the context of clear, positive messaging and integration with delivery of other services that meet young women's needs (e.g., HIV testing, fertility control services that include family planning, emergency contraception, termination of pregnancy where legal, screening and treatment of sexually transmitted infections, pre-natal care, post-exposure prophylaxis, social support and referrals if there is intimate partner violence, and occupational skills training). Other longer acting PrEP formulations (e.g., monthly vaginal rings and long acting injectable agents which may be dispensed every two or three months) are in clinical development and do not yet have demonstrated efficacy. If shown to be effective, these products may have higher uptake, acceptability and adherence than daily pill-taking. *For now, daily oral TDF-based regimens are the only available evidence-based HIV prevention option for young women at high risk of acquiring HIV infection who have limited agency to negotiate the "ABCC" safer sex practices with their sexual partner(s).*
- c) There are several steps that governments, donors and healthcare workers can take to directly improve outcomes for this key population at the individual level that can impact current epidemic trajectories in the region. These steps include being able to identify high HIV-risk young women and to offer acceptable HIV testing services and interventions as appropriate, including social support grants when available, access to schooling, non-

judgmental counseling on sexual and reproductive health and relationships, gender-based violence counseling and referrals, mental health and substance abuse screening, contraceptive and pregnancy service provision, termination of pregnancy service provision where legal, screening and treating sexually transmitted infections, providing access to PrEP and to antiretroviral treatment for HIV positive young women, and delivering these services in the context of accessible youth-friendly services. Novel approaches to enable availability and access to services should be supported in schools and through mobile services and adjusting clinic hours to accommodate employed and/or young women in school.

- d) In settings where PrEP is not accessible or available and/or no PrEP policy is in place, demonstration projects and studies of the operational aspects of PrEP implementation in diverse settings should inform policy and programmatic scale-up of PrEP in all populations and particularly for young women and adolescent girls.
- e) Early adopters of PrEP in young women could serve as peer recruiters, key informants and adherence supporters for other young women and/or their sexual partners for diffusion of the intervention into this key population and sexual networks.

Thus, targets and metrics for PrEP implementation should be identified by PEPFAR in conjunction with the DREAMS countries. 100% of DREAMS countries should have PrEP delivery in 2016 with a geographic prioritization of delivery to counties, provinces or districts with the highest HIV prevalence and incidence among young women. Given the limited availability of evidence-based prevention interventions for young women, PrEP delivery at scale should be a priority to achieve the population-level impact of DREAMS. PrEP needs to be delivered as part of combination prevention with interventions to target men for HIV testing, care and prevention, including MMC and PrEP for men at substantial risk of HIV. In the 2016-17 timeframe of the DREAMS initiative, robust PrEP delivery systems should be established during 2016 in all DREAMS countries and explicit targets identified for young women per county (e.g., at least 10% of young women on PrEP in high HIV prevalence and incidence settings by 2017, which needs to be tailored to the epidemic context).

2. Prioritize PrEP delivery for other key populations:

In addition to focusing on PrEP for young women in Africa through the DREAMS initiative, the EWG recommends PrEP implementation through PEPFAR programs and in partnership with the Ministries of Health for the following key populations, which would improve access to and enhance the impact of PrEP, reduce stigma of using PrEP, and provide unique opportunities for cross training on cultural sensitivity and meet the prevention needs of other key populations. Of note is that like young women, these key populations face the challenges of moral and judgmental attitudes and in some instances their identification as a sex worker, IDU or MSM could lead to discrimination, including incarceration. In implementing PrEP, it is important to recognize the legal status of key populations in countries that PEPFAR is working in and facilitate access to HIV prevention and treatment services to these key populations who are not typical users of public sector health facilities. As with young women, early adopters of PrEP from these key populations could serve as peer recruiters, key informants and adherence supporters. Partnerships with community-

based civil society structures and advocacy groups who are able to reach these hard to reach vulnerable populations will be critical to implementation success.

2a. PrEP as a bridge to ART and viral suppression among HIV serodiscordant couples

Known HIV serodiscordant couples are an important population for HIV prevention and PrEP in Africa. Notably, approximately 50% of partners of HIV-infected persons are HIV-uninfected, frequently are unaware of their serodiscordant status, are at high risk of HIV transmission, and account for a substantial number of new HIV infections.

- Couples HIV counseling and testing should be strongly promoted in HIV clinics and other testing programs with support for disclosure in order for both partners to be aware of each other's status. In settings where co-habiting and serial monogamous relationships are common, strategies to promote knowledge of HIV status are an important entry point for prevention and treatment services.
- HIV serodiscordant couples are often weighing fertility desires with concerns about HIV transmission, and PrEP offers an effective strategy for reducing HIV risk during conception efforts.
- PrEP can be used as a time-limited 'bridge' to ART initiation and viral suppression among HIV serodiscordant couples, virtually eliminating HIV transmission.
- While PEPFAR and other programs recommend partner testing for HIV-infected persons in HIV care, partner testing is not routinely offered, in part due to not having specific services to offer HIV-uninfected partners. PrEP provides an additional rationale for partner testing in HIV care programs and is a cost-effective, time-limited HIV prevention strategy in this key population and in relationships where partner status is unknown or where the existing "ABCC" approach is not feasible.

2b. Female sex workers (FSWs)

FSWs are often at high risk of HIV transmission from their stable partner as well as clients, and account for a substantial proportion of new infections particularly in concentrated and generalized epidemic settings.

- Several African countries where sex work is not criminalized have HIV care, treatment and prevention programs established for FSWs, which could be utilized to offer PrEP to FSWs along with STI testing and treatment, condom promotion and harm reduction strategies. PrEP demonstration projects are underway and planned for FSWs in East and West Africa and southern Africa, which will inform PrEP delivery to this key population.

2c. Men who have sex with men (MSM)

Some MSM have high HIV prevalence and incidence in urban centers in East and southern Africa. PrEP has been demonstrated to be a highly effective intervention for MSM in both efficacy trials and effectiveness studies, and should be included as a key prevention intervention for African MSM in combination with STI testing and treatment, condom promotion and risk counseling.

2d. People who inject drugs (PWID)

Injection drug use appears to be increasing in some urban centers in Africa. PrEP has been demonstrated to be highly effective for IDUs who are at risk of HIV through parenteral and sexual exposure. PrEP should be offered to IDUs as part of combination prevention, including clean injection equipment, opiate substitution therapy, STI testing and treatment, condom promotion, and risk counseling.

Recommendations for PrEP Delivery

PEPFAR should utilize the partnerships in place with governments, advocacy groups and civil society structures and use its strategic partner advantage to catalyse, support and facilitate the introduction of, access to, and provision and promotion of PrEP in the context of country responses to the HIV/AIDS epidemic. These could include awareness raising, demand creation, establishment of systems for PrEP delivery and evaluation of the impact of PrEP provision on new HIV infections. These are elaborated on below:

1. Partner with and support host governments and civil society structures including Non-Governmental Organizations (NGOs) & Community-Based Organizations (CBOs) in PrEP policy formulation, programmatic implementation, and advocacy:

- Engage and partner with civil society to address stigma and cultural barriers to HIV testing and PrEP implementation and to build support for PrEP use and implementation.
- NGOs and CBOs in host countries to get buy-in to PrEP, as well as facilitating sustainability through common messaging, demand creation strategies, marketing and positioning of PrEP.
- Partnerships with local governments, NGOs & CBOs and users to identify most appropriate PrEP delivery models for their country, and facilitate programmatic scale-up and synchronization of PrEP implementation within existing programs and prevention efforts.
- Specific activities that would be useful to support PrEP activities in PEPFAR include support for national and subnational modeling of HIV prevalence and incidence and budget modeling for targeted PrEP delivery, meeting with local government and non-government leaders, particularly in DREAMS countries, to foster national engagement in PrEP planning, delivery and evaluation, and provide updates and support local government, faith-based organizations, policy-makers, provider groups and other key decision makers to enable and support PrEP access. National engagement and support will be critical for the success of PrEP delivery.
- Engage media to increase awareness and accuracy of media coverage about PrEP.

2. Provide flexibility in PrEP drug selection:

- Offer daily dosing of either oral TDF and/or TDF/FTC. Allow flexibility in drug selection in implementation at a country level.
- Choice of TDF or TDF/FTC for PrEP should be guided by the drugs approved for HIV treatment in-country.
- Given the very limited availability of TDF alone or co-formulated TDF/FTC in many PEPFAR countries, the availability of TDF/3TC for PMTCT and PEP, and the similar pharmaco-availability of 3TC and FTC in heterosexual populations, TDF/3TC is an acceptable alternative to TDF/FTC for PrEP.
- Offer both generic and patented drugs, as in some instances generic medication can lower costs, particularly beyond the duration of Gilead donations or in settings where patented drugs are not available or accessible. Ensure messaging and promotional material accurately reflects the drugs that are being utilized at a country level to minimize confusion.
- Ensure supply chain systems are in place to enable continuity of drug access and linked, where possible, to ARV treatment access.

3. Facilitate and support licensure of TDF-based PrEP in PEPFAR countries, but ensure that licensure does not become a barrier to PrEP implementation:

- While Truvada® the ARV drug currently most commonly used for PrEP, is registered for use in the treatment of HIV in many countries, it is not yet registered for the indication of pre-exposure prophylaxis outside of the USA.
- Lack of registration may create a regulatory obstacle, since the drug may be considered experimental and may require PrEP provision under research conditions, requiring regulatory approval resulting in unnecessary delays in PrEP access to key populations.
- Should countries decide to introduce PrEP as part of their HIV prevention packages, then consideration should be given to guidelines that support off-label use as one mechanism to expedite access to this important new prevention option. In addition, some countries (e.g., South Africa) have legislation that allows the national regulatory authority to give exemptions for use of non-registered drugs based on public health motivation, accompanied by prescribed reporting on use.
- PEPFAR should recommend fast track registration for tenofovir and/or Truvada for PrEP, and could facilitate PrEP drug availability and distribution on an individual country basis, as requested by host governments. Where registration is ongoing, governments could request expedited review as this can be done on the grounds of public health and PEPFAR should support timely completion of the processes. Where registration is not planned and to facilitate and expedite PrEP pilots/implementation projects, PEPFAR should consider, together with local partners, establishment of local MoH memoranda enabling TDF or combination TDF/FTC to be used off label to inform normative guidance and/or local policy formulation.
- PEPFAR should support a safe market for PrEP drugs, using a total market approach. While many will access PrEP at no cost through public-sector programs, there may be a growing demand for PrEP – both among young women at risk and among other key populations – that can be met more effectively through the private sector. PEPFAR can support programs to meet this demand in a way that achieves public health goals and supports sustainable models for PrEP delivery.
- Consider PrEP service models that enable users who can afford to purchase drugs to do so from health facilities or qualified pharmacies or other distribution points if HIV testing can be arranged. This supports a market for PrEP commodities, expands access to those who do not wish to use the public sector, protects donor funds for providing greater PrEP access, and potentially relieves both financial burden and overcrowding on the public sector.
- Identify generic formulations appropriate for PrEP (both with and without emtricitabine) and support market-based interventions to make more or all of these formulations available. Registration is one step, but there may be other barriers to bringing these products to the market that donors can overcome. Landscape analyses can reveal these barriers and identify strategic areas for intervention.

4. Scale up HIV testing and offer PrEP in a variety of delivery settings accessible to key populations:

- HIV testing is the first step in the HIV prevention cascade and different strategies to increase the coverage and reach of HIV testing are needed, including self-testing and community-based testing strategies.

- Have a sufficient horizon for PrEP implementation to ensure adequate time for lessons learned to inform programmatic scale-up. This may require more than the 2 year time frame of the DREAMS initiative.
- Offer PrEP in a variety of contexts, such as private health facilities, prenatal clinics, family-planning clinics to reach sexually-active young women, STD clinics, HIV care clinics (in conjunction with partner testing to identify HIV-uninfected partners), and programs that focus on MSM, FSWs and IDUs, in addition to more structured demonstration projects to reach these key populations. Evaluate the operational and systems aspects of the 'how' and 'where' of PrEP delivery for key populations in different settings.
- In parallel with research projects about personal support that facilitates PrEP uptake, evaluate PrEP service delivery models that are more “real-world” for the purposes of learning “what works” in PrEP delivery.
- Better information is needed on optimal patterns of PrEP use (duration, stopping and starting) in key populations.
- Encourage use of electronic patient databases in HIV clinics, which in addition to facilitating ART delivery and monitoring, can be used to identify HIV-infected persons with a partner of unknown status, in order to promote partner testing and offer PrEP as a bridge to ART initiation in the HIV-infected person.
- Strengthen use of social media to promote all aspects of PrEP as an important new prevention strategy, including addressing challenges such as social norms, stigma and discrimination, promoting knowledge of HIV status, partner testing; safety, access and adherence support.
- Mobile phone apps and social media could additionally be used to reach other populations not in care, including young women, with HIV risk assessment and preventive health messages, PrEP-specific information, and adherence support as appropriate for potential users.

5. Recommend simplified and pragmatic safety monitoring for PrEP delivery in PEPFAR

To date no major safety concerns have been identified in PrEP trials to date, hence a pragmatic approach for safety monitoring of PrEP is to keep it simple and focused to facilitate safe, expeditious and effective delivery.

5a. Baseline HIV testing

- Use available in-country HIV testing algorithms
- While 4th generation antigen tests, when available, are beneficial for guiding counseling and facilitating earlier diagnosis and treatment, such tests should not be a pre-condition for PrEP.

5b. Renal monitoring

Given that PrEP is likely to be provided through demonstration projects in the PEPFAR supported countries initially, in the absence of country level guidelines we propose an initial conservative approach for renal monitoring until additional data and guidance are available:

- Make PrEP renal monitoring at a similar level to ART treatment monitoring for TDF containing regimens.
- Whenever possible, follow WHO guidelines which currently propose creatinine

testing at baseline and every 3 months for 12 months then every 12 months if such testing is available. These guidelines will be revised as new information becomes available in the coming year.

5c. Bone density monitoring

- Bone demineralization has been small, does not progress, and was not associated with excess bone fractures. Therefore baseline and ongoing monitoring of bone demineralization is not recommended in PrEP provision.
- Some experts recommend focused studies of bone mineral density in young women who use PrEP for an extended period, as efficacy trials showed a modest and reversible reduction in bone mineral density, adolescent women have not reached their peak bone mass, and because there is limited PrEP use data in adolescent women.
- The data from PrEP demonstration projects should be reviewed and, if indicated, this recommendation could be revised accordingly in addition to use of any specific guidance that may emanate from WHO and/or governments in PEPFAR countries.

5d. Hepatitis B testing

- Hepatitis B surface antigen testing would be helpful but should not be required to start PrEP. HBsAg testing helps identify people who could benefit from Hepatitis B treatment.
- Countries should not have to develop laboratory testing for hepatitis B monitoring in order for PrEP to be implemented.
- When hepatitis B testing is conducted, those who are hep B seronegative should be offered hepatitis B vaccine, but this should not be a requirement for initiating PrEP.
- PEPFAR PrEP recommendations should allow countries to choose an approach that accommodates countries existing hepatitis B monitoring programs for HIV and HBV treatment.

6. Recommend a public health approach to PrEP introduction and delivery

6a. Utilize a public health approach as recommended by the WHO, including: a)

Epidemiologic analyses to identify populations and geographies where PrEP would have the greatest impact on a national and subnational basis; b) Test different PrEP delivery models focusing on integration with other effective prevention services (e.g., family planning services, and STI screening and treatment); and c) Monitor PrEP delivery in terms of the characteristics of PrEP users, uptake of other preventive services, and outcomes of HIV, STIs, and pregnancy.

6b. Intensive adherence monitoring as currently utilized in randomized controlled trials may not be necessary or feasible for a public health PrEP strategy. Simple adherence monitoring is recommended (e.g., pharmacy refills with drug level monitoring only for selected sub-studies/sites) in order to not compromise programmatic scale up of PrEP by making adherence monitoring too complex or too costly to implement in public and private clinics.

6c. Provide client-centered and evidence-based adherence support

- Adherence is fostered by providing information about how well PrEP works when taken, and that the benefits of PrEP require daily use. Messages that PrEP is more than 90% effective when taken are consistent with available evidence. In fact, there are cohorts of men and women in which no HIV infections occurred if PrEP is taken daily.
- Daily use of PrEP is best fostered by linking PrEP taking with a daily habit (e.g., breakfast, a cup of tea or coffee, brushing teeth, or waking up).
- People starting PrEP should be notified that some side effects can occur, including nausea, abdominal cramping, headache, or tingling sensations. Such side effects are typically mild and resolve in the initial few weeks of PrEP use. Side effects can be minimized by taking PrEP with food or at bedtime.
- Weekly SMS reminders for adherence have been helpful but are not required.
- Persons who recognize their risk of HIV exposure are likely to be more motivated to take PrEP with high adherence, some users of PrEP will need adherence support, and that given that risk is dynamic, providers should periodically re-assess risk and perceived need among PrEP users.
- Ongoing PrEP demonstration projects should evaluate PrEP adherence support strategies, and the data should be used to inform adherence support recommendations.

6d. Adherence monitoring

- Pharmacologic monitoring (e.g., tenofovir levels in plasma, dried blood spots) can be useful in the context of demonstration projects, but add cost and complexity to PrEP delivery, and are not recommended for routine use.

7. **PrEP during conception, pregnancy and breastfeeding**

- Given high rates of unwanted and/or unplanned pregnancies among teenagers and higher maternal morbidity and mortality in adolescents, prevention of unplanned pregnancies through provision of family planning services and TOP referral where legal is an important first step.
- Data from Partners PrEP indicate safety in women who became pregnant with no increase in adverse pregnancy or infant outcomes.
- Given high HIV incidence rates during pregnancy and post-partum in PEPFAR and DREAMS countries access to PrEP during pregnancy and post-partum is important to keep HIV uninfected pregnant women uninfected through and following their pregnancies.
- Women who are pregnant or intending to become pregnant and who are at substantial risk of HIV should receive counseling about PrEP efficacy, safety overall and in pregnancy (based on no increased adverse pregnancy or infant outcomes with PrEP use in Partners PrEP). Recent studies suggest tenofovir-based ART regimens in HIV-infected mothers may be associated with a small reduction in lower birth weight and bone mineralization in infants. It is important to continue to collect data on the safety and effectiveness of PrEP use in pregnancy including both maternal and infant outcomes.

8. **Identify provider training needs and develop provider training for PrEP delivery**

- Identify provider training needs regarding risk assessment, counseling about PrEP efficacy, safety and adherence, and PrEP delivery (e.g., HIV and creatinine monitoring, adherence support and monitoring)

- Develop brief PrEP training modules that can be delivered on-line and through continuing education courses.
- Foster train the trainer models where sites that have experience in PrEP offer training in working with key populations, counseling, and PrEP delivery.
- Ensure initial and ongoing training highlight the importance of addressing stigma and discrimination and establishing and supporting supportive environments for HIV/AIDS impacted populations.

9. Conduct sentinel surveillance for monitoring PrEP use

- Routine data collected can be used to monitoring PrEP uptake and patterns of use. Explore what existing electronic or paper ARV treatment monitoring systems are in place.
- The feasibility of expanding the database to include a few key PrEP use variables, such as demographic characteristics, PrEP uptake, sexual practices, patterns and duration of use, should be assessed. A key metric of impact is whether PrEP is preferentially taken up by people with highest exposure to HIV.
- In programmatic scale-up, there should be sentinel evaluation of all people who become HIV infected within 3 months of receiving PrEP medications. Such surveillance would optimally include analysis of drug resistance and TDF drug concentrations at the time of the first laboratory evidence of HIV infection. Dried blood spots are the most convenient and best validated biomarker of PrEP use. Genotypic resistance tests can be performed on dried blood spots as well. Surveillance for drug resistance monitoring needs to be included, and could be built into existing ARV resistance surveillance introduced for ARV treatment monitoring.
- Pharmacovigilance systems should be aligned with existing national ARV treatment surveillance strategies.
- Pharmacovigilance in sentinel sites would be useful to record adverse events when PrEP use in pregnancy with monitoring of maternal and infant outcomes.

10. Conduct implementation research to understand and improve how PrEP is delivered

- The implementation research should be informed at a country or community level by convening key stakeholders such as policy makers, health care providers, beneficiaries and researchers to identify locally relevant implementation challenges that can advance and improve implementation of PrEP by informing, amongst others, how to scale-up PrEP, how to integrate PrEP delivery with other HIV prevention programs and existing services.
- Implementation research should be undertaken using robust and rigorous methodology and be cognizant that implementation success will be dependent on a nuanced understanding of barriers and facilitators at a local level and can include a range of issues such as appropriateness of PrEP for a specific setting; knowledge and awareness of PrEP in priority communities and countries; acceptability and uptake; feasibility of providing PrEP; costs, coverage rates, sustainability of PrEP and the impact of PrEP on overall HIV response
- Where feasible, evaluate HIV incidence as well as process outcomes (characteristics of PrEP adopters and decliners, adherence, alignment of PrEP use with periods of risk, and duration of use).
- Evaluate social marketing strategies and use of social media to increase awareness,

demand creation and motivate persons at substantial risk of HIV to initiate PrEP.

- Establish whether ongoing creatinine monitoring is required for safe PrEP use, and the optimal frequency of creatinine monitoring is not known. Use implementation research to compare outcomes with and without creatinine monitoring, or which creatinine monitoring only at baseline and after 6 months.
- Identify provider and user training needs for risk assessment in HIV-uninfected persons and PrEP delivery.
- Evaluate strategies to reduce the frequency of visits (e.g., use of HIV self-testing).
- Assess use of pharmacies for PrEP supply and resupply to reduce provider burden as well as clinic visits and opportunity costs for persons who have demonstrated motivation and ability to use PrEP.
- Evaluate brief and scalable adherence support strategies.
- Conduct cost and incremental cost-effectiveness studies on different PrEP delivery strategies in different populations and contexts.
- Conduct time and motion studies with health providers and users to improve efficiency of service delivery from both perspectives.
- Evaluate whether women who use PrEP are more likely to use contraceptives and whether contraceptive users are more likely to use PrEP than non-contraceptive users.