

The PrEP Implementation Puzzle

Many missing pieces

What happens if pre-exposure prophylaxis or, PrEP, works?

Although we love illustrations like the one that shows PrEP, or any other new intervention, fitting into the big picture of existing programs and strategies (see opposite page), the reality is nebulous. Different PrEP trials could have different results. Even if one or more of the ongoing PrEP trials shows protective benefit—and this is by no means guaranteed—there isn't a neat, PrEP-sized slot sitting vacant in the vast puzzle of the AIDS response. Instead, plans for PrEP introduction must address many of the missing or incomplete pieces of the AIDS response to date.

A strategy like PrEP or a topical ARV-based microbicide involves issues that set it apart from a non-ARV microbicide like PRO 2000 or from a vaccine. An HIV test is not needed for counseling about using a male or female condom. If a person becomes infected with HIV after male circumcision or, hypothetically, after using a microbicide like PRO 2000, these previous prevention strategies won't have any bearing on treatment options. PrEP is a different story altogether. This article considers some of the reasons why.*

PrEP and other forms of ARV prevention, like topical ARV-based microbicides, would require HIV testing and counseling for the HIV-negative individual using them. The details of program design are impossible to forecast, but we assume that providing ARVs to someone HIV-negative would happen in the context of regular HIV testing to minimize the risks of developing drug-resistant virus should the person acquire HIV while using an ARV-based prevention method. (HIV-positive people using one or two ARVs for prevention would in effect be receiving suboptimal HIV treatment and run the risk of developing drug resistance.)

Using ARVs for prevention in HIV-negative people will require substantial investments and innovative programming around HIV testing, delivery of integrated services, and community education.

The same goes for use of ARVs to reduce HIV-positive individuals' risk of transmitting the virus. This "treatment-as-prevention" approach posits that reducing viral load will reduce infectiousness and therefore slow rates of transmission. With ARV-based prevention in HIV-positive people or PrEP in HIV-negative people, the potential prevention benefits won't come without serious attention to a range of cross-cutting issues.

For both PrEP (should it work) and treatment-as-prevention for HIV-positive people, specific work is needed in the areas of:

- Human rights
- HIV testing
- Health care infrastructure
- Financing
- Comprehensive programming

* This article is adapted from "Life in the ARV Generation," a forthcoming AVAC publication that looks in-depth at the benefits and pitfalls that could come with using ARVs as prevention tools for HIV-positive and/or HIV-negative people. Look for the publication at www.avac.org.

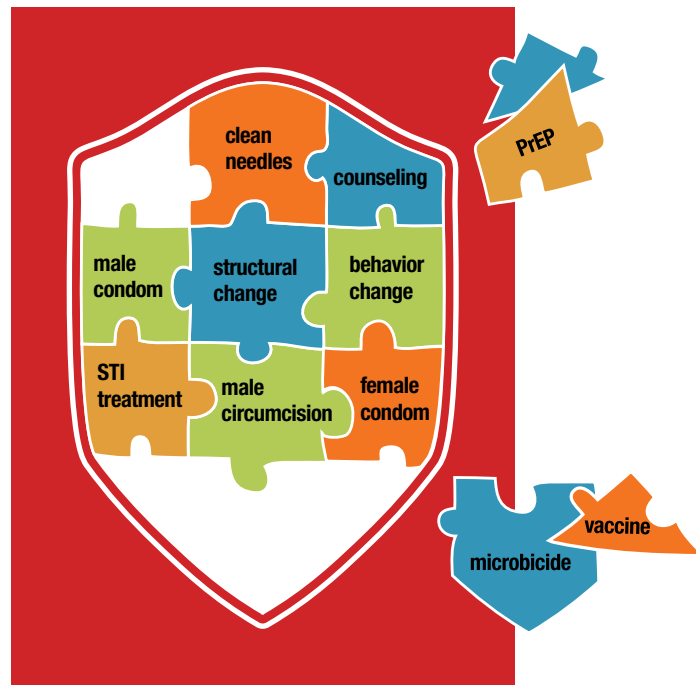
Human rights

ARV use by both HIV-positive and HIV-negative people may prove valuable in HIV prevention (see table on page 50 for more explanation of these different approaches), but it will not solve the fundamental individual, social, logistic, or political challenges that complicate prevention programming. We have to guard against letting the power of a drug seduce us into ignoring the personal and social complexities of vulnerability to HIV. Personal choice is of central importance in health care, and it is imperative to provide interventions that first and foremost serve the patient.

There is growing recognition that HIV prevention efforts have focused too much on individual decision-making and not enough on the social and environmental context of vulnerability to infection. HIV prevention approaches often assume that given accurate information and tools like male and female condoms, people rationally choose to protect themselves. Yet the reality is much more complex for many people, for example, for women who do not feel they have equal power in their relationships, or gay men and other men who have sex with men (MSM) whose sexual behavior is illegal and are constrained to have furtive sexual contacts.

If PrEP has a high level of efficacy in trials, then ARV-based prevention programs might be aimed at high-risk groups, potentially emphasizing individual choice and behavior change at the expense of social context and structural factors that contribute to HIV risk. Even if delivery is not targeted, people taking ARV prophylaxis may be assumed to be in a high-risk group, subjecting them to stigma and discrimination.

The Proven and Possible Puzzle Pieces of Prevention



PrEP—which involves ARV use in HIV-negative people—will have one set of testing considerations. The treatment-as-prevention approach, which suggests early ARVs for HIV-positive people to reduce viral load and therefore infectiousness, will have another. There's an ongoing trial in serodiscordant couples that is looking at the impact of early treatment of the HIV-positive partner on transmission risk, which could provide evidence in addition to the observational data that already support this strategy. If there is a sea change, and treatment-as-prevention gains traction among programmers and policy makers, it could lead to intense pressure on individuals to accept HIV testing so that public health authorities can identify as many people living with HIV/AIDS (PLWHA) as possible. PLWHA may come under pressure to treat early, whether or not they want to start ARVs. While

“Surveys in sub-Saharan Africa have shown that a median of just **12%** of men and **10%** of women had been tested for HIV and received the results.”¹

Sub-Saharan Africa

expanded treatment delivery is a good thing, coercion in health care undermines autonomy, a pillar of medical ethics, and threatens to drive people away from health services.

HIV testing

Any discussion of expanded use of ARVs for prevention has to start with a clear-eyed reckoning of the state of HIV testing worldwide. In the era of ARV-based prevention, an HIV test would be the gateway both to treatment and to comprehensive prevention services. Individuals using PrEP or ARV-based microbicides would also need regular HIV testing to determine whether they had become infected. The frequency of this testing is already being debated in the scientific literature. We feel strongly that community perspectives on testing and other aspects of service delivery for PrEP should help shape context-specific programs if they are warranted by clinical trial data. It's premature to make recommendations about introduction of widespread genotyping and resistance testing should PrEP show any benefit. It will be essential to gather information on the emergence (and waning) of detectable drug-resistant virus in people using PrEP who become HIV-positive. These data can help guide long-term strategies.

Expanding access to HIV testing is clearly a good thing. The challenge is to surmount the many logistical, human-resource, and financing hurdles involved, while minimizing potential negative outcomes of testing like stigma, discrimination, violence, and breaches of confidentiality. In 2008, the World Health Organization (WHO) reported that although HIV testing coverage rates had increased over the previous two years, they remain very low in many areas with serious HIV epidemics. How low? The statistics and facts on this page and throughout the section are glimpses of the shortfall in different contexts.

Unless access to and utilization of HIV testing expands, the impact of PrEP and early treatment in HIV-positive people will be greatly limited. There are numerous approaches to reaching more people with HIV testing, and ideally HIV testing will increasingly be included in scaled-up systems of comprehensive primary care. Since 2007, WHO has recommended that HIV testing and counseling be offered on a routine basis to everyone who uses health facilities in countries with generalized HIV epidemics (i.e., epidemics that have spread beyond subgroups to at least one percent of the general population). The agency says that provider-initiated testing and counseling has met with generally high acceptance, but it acknowledges challenges with protecting confidentiality of test results and with potential negative consequences of disclosure of results, including violence and stigma. Several other models for broadening access to HIV testing have demonstrated success in increasing testing rates, yet human rights concerns about expanded testing remain.^{2,3}

¹ UN, World Health Organization. Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities. 2007 May. Online. UNHCR Refworld. Available at URL: <http://www.unhcr.org/refworld/docid/467f952f2.html>

Health care infrastructure

ARVs might not do for prevention what they have done for treatment, given the many stumbling blocks in delivery of ARV treatment. Scale-up of AIDS treatment access has in many ways been a success, reaching over three million people with lifesaving drugs in low- and middle-income countries. Yet, five years after the WHO set an ambitious goal to greatly increase access to AIDS treatment, these drugs remain out of reach for an estimated 69% of people in need.⁴ This includes millions of people in rural areas with limited or no access to health care facilities, marginalized populations who fear coming forward for treatment, and children who need tailored treatment approaches. There are also major infrastructure challenges in health care human resources, sustainable procurement mechanisms, laboratory capacity, and other areas.

Financing

ARVs used in prevention may remove some barriers between prevention and treatment, but additional costs for drug purchasing (both PrEP drugs and ARVs for treatment that could be used by PrEP users who become HIV-infected and acquire resistance) and delivery will put new strains on overburdened health budgets, health systems, and human resources.

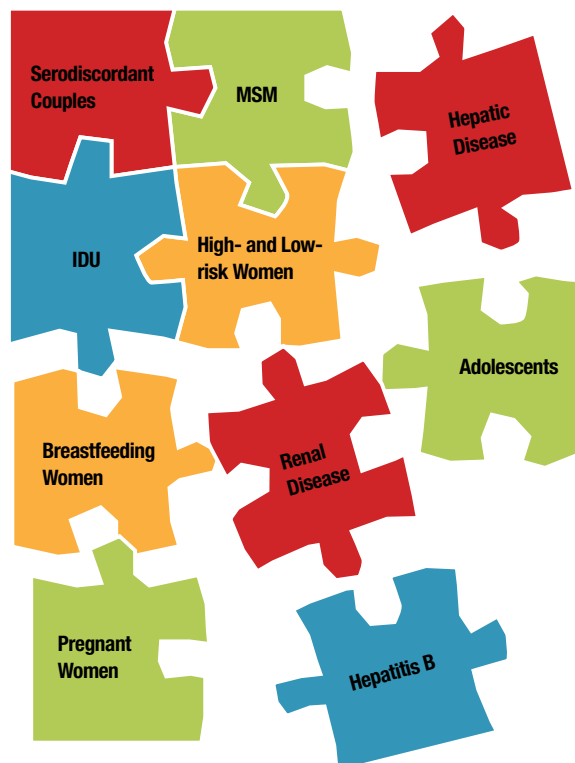
Comprehensive programming

A comprehensive package of HIV prevention interventions will be needed alongside

ARV-based approaches. Behavioral HIV prevention programs will need to be infused with new messages and approaches appropriate for the new context. There also needs to be an informed decision-making process to determine where ARV-based prevention approaches should be used for greatest public health impact.

Many stakeholders have argued that if PrEP shows a benefit that warrants its introduction, delivery will need to be carefully targeted to maximize its impact and make it cost-effective. But personal choice will be a central factor in use of PrEP as well. Helping individuals assess

Studies to Complete the PrEP Puzzle



² AIDS & Rights Alliance for Southern Africa (ARASA) and Human Rights Watch. A Testing Challenge: the Experience of Lesotho's Universal HIV Counseling and Testing Campaign. 2008 Nov. Available from URL: <http://www.hrw.org/en/reports/2008/11/18/testing-challenge>

³ Abdool Karim Q, et al. The influence of AIDS stigma and discrimination and social cohesion on HIV testing and willingness to disclose HIV in rural KwaZulu-Natal. *South Africa Global Public Health*. 2008; 3(4):351-365.

⁴ WHO, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: Progress Report. 2008. Available at URL: http://www.who.int/hiv/pub/towards_universal_access_report_2008.pdf

Table 2 ARVs Now and in the Future

Intervention	Description	Status	Key Issues
Current uses of ARVs in HIV-positive and -negative people			
HIV treatment	ARVs used in combination inhibit HIV entry into cells or replication within cells, reducing viral load	As of 2007, 31% of the nearly 13 million people needing HIV treatment were receiving it.	<ul style="list-style-type: none"> Challenges in reaching rural and marginalized populations Need for adherence and other supports
Prevention of vertical transmission	ARVs given to a pregnant woman during pregnancy and to the infant at birth greatly reduce the likelihood the newborn will become infected with HIV	As of 2007, 34% of HIV-positive pregnant women were receiving ARVs to prevent mother-to-child transmission.	<ul style="list-style-type: none"> Challenges with access and uptake due to stigma and limited access to healthcare system Need to ensure pregnant, postpartum and breastfeeding women receive appropriate care and other services Need clarity about use of ARVs with breastfeeding
Post-Exposure Prophylaxis (PEP)	ARVs given soon after high-risk potential exposure to HIV are thought to significantly reduce the likelihood of infection	PEP is used mainly in the case of health care worker exposure, though is available more broadly in some industrialized countries.	<ul style="list-style-type: none"> Inability to do randomized clinical trials Need to begin month-long regimen soon after exposure
Strategies being researched			
Oral Pre-Exposure Prophylaxis (PrEP)	ARVs taken regularly or before and after exposure might reduce the likelihood of infection	Seven current or planned clinical trials of PrEP. The first efficacy trials may report data as early as the first quarter of 2010.	<ul style="list-style-type: none"> Need for additional research on: intermittent (vs. daily) use; long-term toxicity and drug resistance; adherence; use by pregnant women and adolescents Need to plan for targeted rollout Will require expanded and frequent HIV testing Need to develop new agents for potential use in PrEP
ARV-based microbicides	ARVs used in gels, films, vaginal rings or other products that would be inserted in the vagina or rectum to reduce the likelihood that the user becomes HIV infected during sex	The first efficacy trials may report data as early as 2010.	<p><i>All issues with oral PrEP above, and:</i></p> <ul style="list-style-type: none"> Need to optimize vaginal and rectal delivery methods to maximize acceptability Need for more research on potential rectal use
Emerging uses of ARVs as prevention in HIV-positive people			
Treatment as prevention and earlier initiation of treatment	ARV treatment of people living with HIV may reduce their infectiousness	<ul style="list-style-type: none"> Growing body of evidence suggests earlier ARV treatment initiation benefits the patient, but effects of immediate treatment in those who don't need it are unknown. Swiss Commission on AIDS-Related Issues released statement in 2008 arguing that PLWHA on treatment and with no STIs are sexually non-infectious. NIH study, HPTN 052, on earlier initiation of treatment and infectiousness to report results in 2014. 	<ul style="list-style-type: none"> Concerns that assumptions about non-infectiousness will lead to increased risk taking, undermining prevention effect Need to update global policy to initiate treatment earlier and measure prevention impact Need to confirm lower HIV viral load (VL) in blood correlates with reduced infectiousness given that VL can be measured in seminal fluids of some men with undetectable VL in blood
Testing and immediate treatment	Theoretical model suggesting that widespread HIV testing and immediate treatment of all those identified as HIV-positive would greatly reduce HIV incidence	Article in <i>The Lancet</i> (Nov 2008) proposed model and said WHO will hold consultations in 2009.	<ul style="list-style-type: none"> Enormous logistical challenges in scaling up HIV testing and immediate treatment Need to determine whether immediate treatment is medically optimal for PLWHA



Even if multiple studies show that PrEP reduces HIV transmission, there will be much to be done before global implementation:

- Additional research on delivery, impact, safety, alternative dosing and other issues
- Increased counseling and testing
- Expansion of innovative, integrated HIV prevention and treatment programs
- Collaboration with communities to develop introduction strategies and identify groups to benefit most

their personal risk for HIV infection will likely be a critical element of successful PrEP programs because these assessments will help guide an individual's decision-making. Issues that might be weighed include the risks and benefits of taking an ARV for prevention; individual ability to take PrEP as prescribed; and the duration an individual might spend on PrEP.

Even if PrEP or other forms of ARV-based prevention are highly effective, they are unlikely to provide 100% protection from infection or transmission. Current HIV prevention approaches—including male and female condoms, clean needles, male circumcision, HIV education and behavioral interventions, and safe blood supplies—will remain essential to controlling HIV incidence and will need to be part of a package of prevention services. One worry is that policy makers, public health leaders, and donors, captivated by the availability of a drug to prevent infection, will invest in ARVs at the expense of other effective interventions. Community-based HIV educators will need training to play an active role alongside health care workers in dispensing ARV-based prevention.

To get prepared, we need to acknowledge the urgent actions needed by virtually every stakeholder group working in the field.

Recommendations

- ✦ **The research community needs to invest much more time in understanding how ARV-based prevention could best be used in real-world situations, in addition to testing whether particular drugs work in the context of a clinical trial.** This means an increased emphasis on the types of programs that might be used to deliver PrEP, drawing on the expertise and priorities of implementers and service providers. Some of this can happen before there are results from PrEP trials. If findings warrant introduction of PrEP, then systematic research, monitoring, and post-marketing must take place to learn more about safety, including renal and hepatic issues and drug resistance, and about delivery strategies.
- ✦ **Funders, researchers, and community stakeholders need to clarify and execute a research agenda to address questions that may not be answered by current trials.** What types of intermittent dosing strategies will offer protection for users

who are unwilling or unable to take PrEP every day? What will current trials tell us about this, through adherence and blood-level data? What else could be gathered from current effectiveness trials and/or small trials that might be launched while the large studies are ongoing? More research is also needed on rectal microbicides.

- ✦ **Public health leaders, funders, community advocates, and researchers need to develop a strategic plan of action for piloting delivery of PrEP in various settings.** What should initial programs look like? What's the best way to integrate PrEP into existing services and to provide clear messages to all audiences, while perhaps only delivering to targeted populations? What bridging and long-term safety research should be built into programs so that data are gathered during rollout?
- ✦ **Funders must explore ARV-based prevention as an opportunity to change the course of the epidemic,** an opportunity requiring early and substantial additional investments that will pay dividends down the road. Although there's no one-size-

fits-all approach to PrEP implementation, it will require substantial investments in HIV testing and an emphasis on integration of prevention treatment and care. Harnessing the prevention potential of using ARVs to reduce infectiousness in people with HIV will also take vision, innovation and substantial resources.

- ✦ **Funders and policy makers (in donor and heavily affected countries) have to be prepared for strategic delivery of PrEP that maximizes public health impact.** Mathematical modeling and cost-effectiveness studies are needed to define best approaches for targeted delivery of PrEP and other interventions in different epidemic settings. An access plan is needed that anticipates purchase capacity, drug registration, and manufacturing and delivery of PrEP and treatment-as-prevention programs. Support is needed for public health research on issues such as how to minimize stigma when identifying and recruiting individuals most at risk for HIV infection. Systems need to be in place for tracking drug adherence, drug resistance, and incidence. The long-term success of ARV treatment programs depends on affordable, reliable access to first-, second-, third-line, and salvage therapy regimens. This would become more critical if ARVs were used for prevention, in order to ensure appropriate treatment options for people who used PrEP and went on to become infected. Normative agencies including UNAIDS and WHO should develop a work plan that includes consultation with multiple stakeholders, development of guidance documents, and assistance to help country governments determine whether and how to use PrEP (see page 54).

Each PrEP Trial is a Piece of the Puzzle

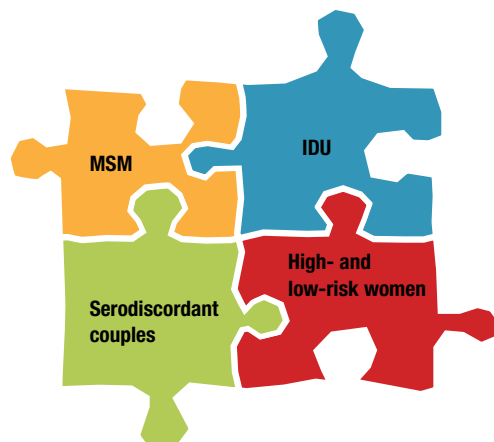
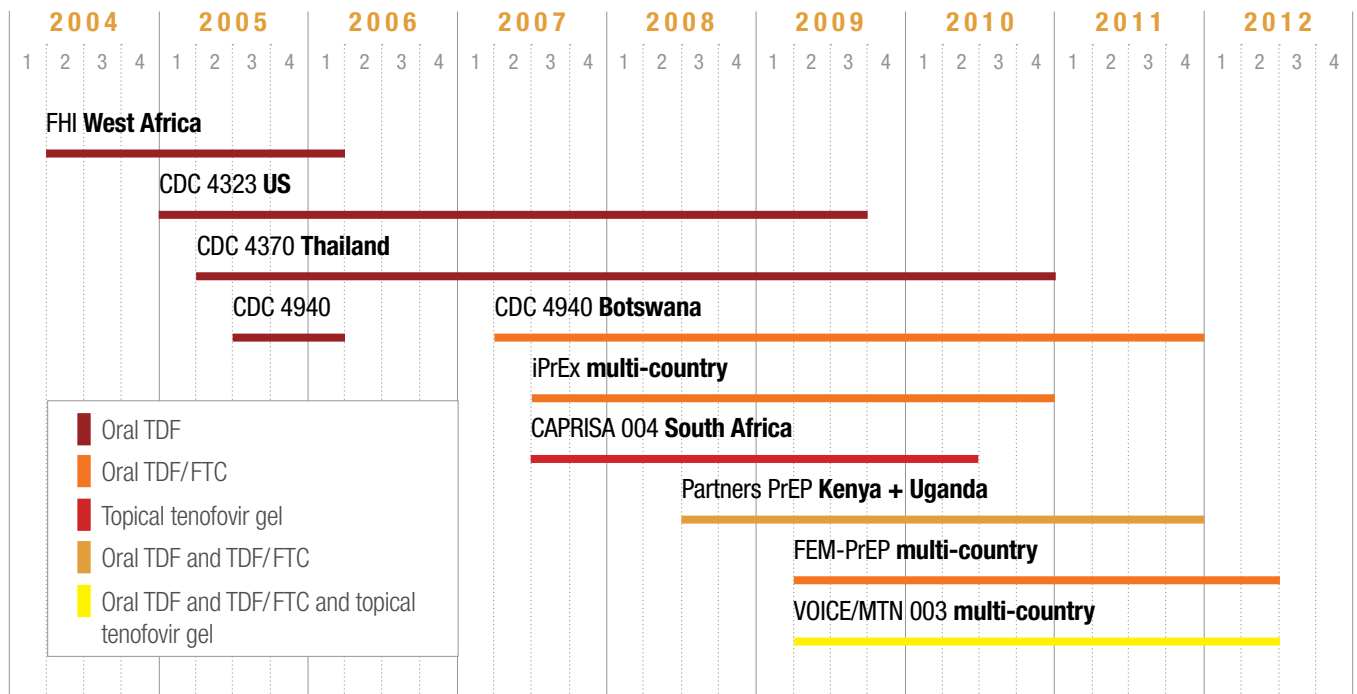


Figure 4 Timeline for Ongoing and Planned PrEP Trials* (May 2009)



* The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor trial progress and will update the timeline accordingly. To view or download an updated timeline visit www.prepwatch.org.

✦ **The pharmaceutical industry should work with global agencies and governments to make sure PrEP will be accessible where needed.** This includes using voluntary licensing and tiered pricing to lower costs, anticipating manufacturing capacity needs, and working with partners to minimize delay in moving ARVs through the drug registration process in heavily affected countries. Pharmaceutical companies should also make new agents with potential use in PrEP or other ARV-based prevention available for testing if they themselves will not test these agents for such applications.

✦ **AIDS and health advocates must articulate an ambitious, balanced agenda for HIV testing, PrEP, and early initiation of treatment in HIV-positive people.** It is time to fully embrace HIV testing and prevention as we have embraced HIV treatment and to help identify how to widely deliver these services in a way that respects human rights and minimizes stigma and discrimination. This will require closer connections among advocates for AIDS treatment, human rights, maternal and child health, and health systems generally. ✦