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# Current and Future PrEP Medications and Modalities: On-demand, Injectables, and Topicals

Matthew R. Beymer[1] · Ian W. Holloway[2] · Craig Pulsipher[3] · Raphael J. Landovitz[4,5]

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## Abstract

**Purpose of Review** Pre-exposure prophylaxis (PrEP) is a potent HIV prevention strategy, but uptake of daily oral PrEP remains low. This review covers PrEP agents currently available and agents and modalities under investigation.

**Recent Findings** Injectable ARV preparations have high acceptability among users but are likely to require adherence to 8-week interval injections. Topical microbicide gels and vaginal rings have underperformed by intention-to-treat analyses in efficacy studies, at least in large part due to challenges with adherence and/or sustained use. However, daily oral TDF-FTC also underperformed in randomized, placebo-controlled trials compared to expectations and subsequent real-world pragmatic use.

**Summary** On-demand (2-1-1 dosing strategy for MSM) and injectable PrEP appear to be acceptable among participants in clinical trials. These modalities are particularly compelling alternatives for individuals who either do not want to take a daily medication (both on-demand and injectable) and/or want to take PrEP without a long commitment (on-demand). Emerging modalities such as vaginal films, microneedles, and subdermal implants have numerous advantages but are still in early stages of development.

**Keywords** Pre-exposure prophylaxis (PrEP) · HIV/AIDS · On-demand · Injectables · Microbicide gels · Vaginal rings

## Introduction

HIV pre-exposure prophylaxis (PrEP) is an HIV prevention strategy that has been shown to significantly reduce the sexual transmission of HIV. Models estimate that PrEP confers an HIV incidence reduction of 99% for men who have sex with men (MSM) and ≥ 90% for women, in the setting of consistent daily adherence [1, 2]. The first agent to receive regulatory approval for PrEP is a once-daily oral coformulation of tenofovir disoproxil fumarate with emtricitabine (TDF-FTC). In 2012, daily oral TDF-FTC was approved by the United States (U.S.) Food and Drug Administration (F.D.A.) for MSM, high-risk heterosexuals, and people who use injection drugs (PWID) [3]. In 2018, the indication was expanded to individuals weighing at least 35 kg (approximately 77 pounds) so that younger people could access PrEP [4•]. Outside the USA, TDF-FTC PrEP has regulatory approval in 43 other countries with additional regulatory applications pending (Fig. 1) [5].

In the USA, 1.2 million adults are estimated to have sufficient HIV acquisition risk to warrant PrEP use [6], but uptake has been sub-optimal with only approximately 70,000 unique individuals with an active PrEP prescription in the fourth quarter of 2017 [7]. Among individuals who decide to initiate PrEP, demonstration projects and clinical databases suggest that medication adherence is insufficient to provide high levels of HIV protection among select populations.

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✉ Matthew R. Beymer
mrbeymer@gmail.com

[1] Department of Health and Mental Health Services, Los Angeles LGBT Center, McDonald/Wright Building, 1625 N Schrader Blvd, Room 114-E, Los Angeles, CA 90028, USA

[2] Department of Social Welfare, Luskin School of Public Affairs, University of California, Los Angeles, 337 Charles E Young Drive East, Los Angeles, CA 90095, USA

[3] APLA Health, 611 S Kingsley Dr, Los Angeles, CA 90005, USA

[4] David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA

[5] UCLA Center for Clinical AIDS Research & Education (CARE), 11075 Santa Monica Blvd, Suite 100, Los Angeles, CA 90024, USA

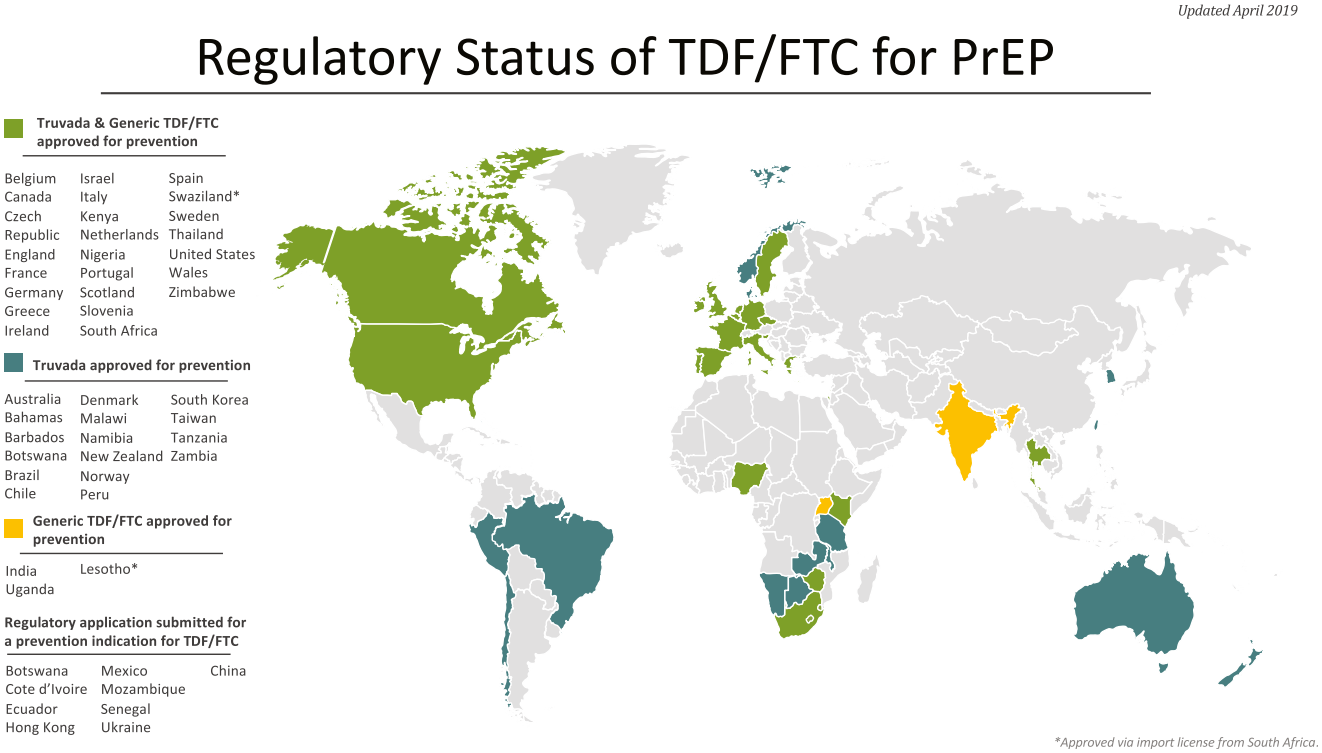


**Fig. 1** Twenty-seven other countries with additional regulatory applications pending

Medication adherence is just one potential barrier toward wider PrEP uptake. Other concerns about daily PrEP include resistance to TDF-FTC compromising first-line HIV treatment options globally. Concerns also exist over the potential for drug-drug interactions, especially for hormones and tuberculosis medications [8]. In addition, TDF-FTC is very safe and well-tolerated, but it does have signature toxicities including gastrointestinal intolerance, renal toxicity, and bone toxicity [9–11]. Particularly among women, gastrointestinal side effects seem to lead to more discontinuations [12]. Therefore, alternative PrEP agents with a similarly safe or better profile are needed. Lastly, the development of different family planning modalities shows that more choices increase the chances of finding a PrEP modality acceptable to a wider audience [13]. These options range from alternative dosing of oral products (both existing and novel); injectable preparations; topical products delivered as gels, rings, films, and long-acting/extended release (LA/ER) systems such as microneedles and implants. The purpose of this manuscript is to review alternative PrEP modalities as well as highlight potential strengths and drawbacks of each approach.

## Currently Available Options

### On-demand/Nondaily PrEP

"On-demand" PrEP is a dosing strategy in which an individual takes oral PrEP only around the time of a sexual event, and is predicated on the ability to plan sexual activity (Table 1). A randomized, double-blind, placebo-controlled trial in France and Canada among MSM evaluated a dosing protocol of a double dose (two tablets taken simultaneously) of oral TDF-FTC (or placebo) between 2 and 24 h prior to sexual activity and then single tablets of oral TDF-FTC at 24 h and 48 h after the first dose, with ongoing daily dosing if exposures continue. Participants randomized to active TDF-FTC demonstrated 86% reduced incident HIV infections compared to those randomized to placebo [14•]. Of note, the median number of doses was 15 tablets per month, approximating the 4 doses per week known to confer high levels of rectal protection during attempted daily dosing—and raising the question as to whether it was the on-demand strategy per se, or the high rates of dosing (regardless of proximity to intercourse) that most contributed to the overall findings. A post hoc subgroup analysis suggests that on-demand PrEP remained effective in participants with less frequent sexual activity [15], and similar results were seen in the open-label extension of the double-blind randomized controlled trial [16]. Current guidelines for on-demand dosing are conflicting and pharmacokinetic (PK) data offer conflicting predictions of on-demand dosing efficacy at least in part due to lack of clarity as to the optimal PK correlate of HIV protection [17, 18]. However, increasing open-label data in follow-up to the initial randomized controlled trial supports the efficacy of the approach, leading to opportunities to individualize recommendations around TDF-FTC dosing regimens [19].

**Table 1** Compounds, phase, and frequency of dosing for investigational HIV pre-exposure prophylaxis (PrEP) modalities

| Modality | Compounds used | Phase | Frequency of dosing | Next phase |
|---|---|---|---|---|
| On-demand/nondaily PrEP | oral TDF-FTC | Post-3 | Pericoital | Regulatory approval in Europe, United Kingdom, and Canada. Pending approval in the United States |
| Oral tenofovir alafenamide with emtricitabine (TAF-FTC) | oral TAF-FTC | 3 | Daily | Pending results of phase 3 efficacy studies |
| Injectable agents | Rilpivirine | 2 | Every 8 weeks | No progression: concerns about cold-chain requirements and a low barrier to resistance |
| | Cabotegravir | 3 | Every 8 weeks | Pending results of phase 3 efficacy studies |
| Topical microbicide gels | 1% Tenofovir Gel (Vaginal) | 3 | Daily | No progression: low observed efficacy |
| | 1% Tenofovir Gel (Rectal) | 2 | Daily and Pericoital | Pending results of phase 3 efficacy studies |
| Vaginal rings | Dapivirine | 3 | Once per month | Open-label extensions are ongoing |
| Vaginal films | Dapivirine | 1 | Pericoital | Additional phase 1 studies |
| | Tenofovir | 1 | Pericoital | Additional phase 1 studies |
| Microneedles/microarray patches | Rilpivirine | 0 | Undetermined | Trials are in the pre-clinical phase |
| Subdermal implants | TAF | 0 | Undetermined | Trials are in the pre-clinical phase |
| | Elvitegravir | 0 | Undetermined | Trials are in the pre-clinical phase |
| Broadly neutralizing HIV-1 monoclonal antibodies | VRC01/VRC01LS | 2 | Undetermined | Pending results of phase 2B efficacy studies |

Further complicating the debate, an open-label phase 2 study among MSM, transgender women, and cisgender women compared the percent of sex acts "covered" by three dosing strategies: daily, time-driven (one dose of oral TDF-FTC twice weekly with a post-sex dose), and event-driven (one dose of oral TDF-FTC before and after sex). Among all populations, daily dosing provided higher rates of "coverage" of sex acts than did event- or time-driven dosing strategies [20, 21], suggesting that routinization of dosing is more likely to result in "coverage." Importantly, no differences in safety were seen across these dosing strategies, disavowing conjecture that less than daily dosing may reduce side effects attributable to daily oral TDF-FTC use.

The advantages of on-demand PrEP are that it could be cost-saving when compared to daily oral TDF-FTC and may be helpful for people who have infrequent sex. Disadvantages include non-routinization, patient education on how to most effectively deploy and use on-demand PrEP, and the potential for unplanned sex compromising the precoital dose [22]. Most importantly, there is an absence of data for transwomen and ciswomen, limiting its potential use only for MSM.

## Modalities Under Investigation

### Daily Oral TAF-FTC

The fixed dose combination of tenofovir alafenamide with emtricitabine (TAF-FTC) is currently under investigation as another form of daily oral PrEP. Macaque challenge models have demonstrated preventive efficacy for TAF-FTC against rectal and vaginal exposures [23, 24]. In contrast, PK studies have demonstrated poor rectal and vaginal tissue penetration [25]. TAF-FTC is currently under investigation for PrEP activity in a phase 3 efficacy study comparing daily oral TDF-FTC to TAF-FTC in MSM and transgender women globally. Results were presented at CROI 2019, and while only 22 infections were observed, incidence rates in both the TAF/FTC (0.16 per 100 person-years) and TDF/FTC (0.34 per 100 person-years) were extremely low despite high rates of incident STIs [26]. Regulatory submissions are under review.

### Injectable Agents

Long-acting rilpivirine (RPV LA) and long-acting cabotegravir (CAB LA) are in advanced development for HIV prevention; both are crystalline, water insoluble nanoformulations for intramuscular injection. Because of their prolonged half-lives, injectable agent use is currently preceded by a 4-week oral lead-in period of a short-acting tablet formulation of the product to assess safety and tolerability.

**Rilpivirine** Rilpivirine, currently approved for HIV therapeutics (in combination with other antiviral agents), is a second-generation non-nucleoside reverse transcriptase inhibitor. RPV LA has demonstrated efficacy in preventing HIV transmission in humanized mouse models [27]. In humans, two phase 1 trials have investigated the safety and PK of RPV LA, demonstrating good tolerability and rapid plasma accumulation after administration [28–30]. A phase 2 trial among women administered 1200 mg of either RPV LA (administered as two 3-mL injection) or placebo every 8 weeks followed participants up to a year after terminal injection. The trial

found no significant difference in side effects or adverse events between RPV LA and placebo treated participants [31, 32]. RPV has not progressed to phase 3 clinical trials, likely out of concerns for cold-chain requirements of the injectable product and a low barrier to resistance.

**Cabotegravir** Cabotegravir is an investigational strand-transfer integrase inhibitor currently in development both for HIV treatment and HIV prevention. CAB LA has been shown in macaque models to provide protection against simian/human immunodeficiency virus (SHIV) challenge via vaginal, rectal, penile, and intravenous routes [33–36]. In phase 2A trials, CAB LA was generally safe and well tolerated; although the majority of participants experienced local injection site reactions, these were overwhelmingly mild to moderate, and infrequently led to product discontinuation [37–39].

Initially studied as two simultaneous gluteal injections of CAB LA (2 mL each, 800 mg total) every 12 weeks [40], at that dose and dose-interval, approximately 30% of participants had injection trough concentrations that were below the protein-adjusted IC90 (1 x PA-$IC_{90}$), the protective threshold established in non-human primate rectal challenge models [34]. In response to these findings, a second phase 2A trial in men and women globally was modified to evaluate an alternative dose of 600 mg (given as a single 3-mL injection) every 8 weeks after an initial 4-week injection interval; this dose/interval was also well tolerated, with similar rates and consequences of injection site reactions [41•]. CAB LA is currently being evaluated in ongoing clinical phase 3 studies to establish HIV prevention efficacy in comparison to daily oral TDF-FTC among MSM, transgender women, and cisgender women globally.

Potential advantages of injectable ARVs include less frequent dosing than oral TDF-FTC as well as the potential for reduced gastrointestinal toxicity [42]. Potential disadvantages of injectable ARVs include the current requirement of an oral lead-in period, injection site reactions, and a prolonged PK tail. The clinical consequences of seroconversion during the PK tail vis-à-vis selection for resistant HIV virus remain to be determined in the phase 3 studies—but have the potential to compromise the activity of integrase-inhibitor based first-line ARV therapy. The need for an oral lead-in period in clinical use will similarly be informed by the accumulating safety experience in phase 2 and 3 clinical trials.

## Topical Microbicide Gels

Topical microbicide gels contain an antiviral product that is applied to either the vagina or rectum in pericoital or daily dosing strategies. In a non-human primate model, both gel with 1% tenofovir (TFV) alone and with 5% emtricitabine (FTC) fully protected macaques from vaginal exposures to SHIV [43]. In a phase 1 study investigating daily application of 1% TFV vaginal gel, the product was well tolerated over a 2-week course with primarily mild adverse events [44].

The first phase 3 study of an ARV-based topical microbicide gel randomly assigned HIV-uninfected women in South Africa to receive either 1% TFV gel or a placebo gel applied vaginally. TFV gel or placebo gel was applied in a pericoital dosing strategy consisting of a first application 12 h before intercourse and the second dose of gel 12 h after intercourse. The TFV gel arm demonstrated a use-dependent 39% reduction in HIV incidence when compared to the placebo gel arm [45]. However, subsequent studies of the 1% TFV gel when dosed daily have shown discrepant results based on adherence and patterns of use. Two phase 3 trials among women using a daily dosing pattern reported no reduction in HIV incidence between treatment and placebo groups [46, 47]. Poor observed efficacy may be explained by low daily adherence.

In phase 2 testing of tenofovir 1% rectal gels (TFV gel), there were no differences in safety profiles between daily TFV gel, TFV gel applied before and after receptive anal intercourse (RAI), and daily oral TDF-FTC [48]. Furthermore, 83% of participants had excellent (≥ 80%) adherence to daily gel and 93% had excellent (≥ 80%) adherence to the pericoital (used before and after sex) TFV gel regimen [49].

Gels may be preferred by some consumers because they have the potential to be dosed intermittently, can act as a lubricant during sex, and may be both more discreet and have fewer side effects when compared to systemic agents. However, gels, similar to other topical agents, would only be expected to provide protection to the local compartment of application, absent being able to achieve systemic concentrations of the antiviral product. Three studies examining the safety, tolerability, and PK of dapivirine gel administered rectally are enrolling or in development.

## Vaginal Rings

The vaginal rings, similar to products used for contraception, are currently in advanced development for HIV prevention. Rings provide a sustained, controlled release of antiviral agents over time. An elastomer ring containing dapivirine has demonstrated safety and tolerability in phase 1 and 2 trials [50–54]. Notably, 96% of participants in a phase 2 study of a dapivirine ring reported that the ring was comfortable, and 97% reported that they would be willing to use this modality in the future if proven effective [54].

Two phase 3 trials investigating dapivirine rings have found similar results with an HIV incidence reduction of between 27 and 31% when comparing treatment and placebo groups [55, 56]. In both trials, there was no difference in the incidence of pregnancy between the dapivirine and placebo groups suggesting no clinically significant drug-drug interactions between dapivirine and hormonal contraception [55, 56].

Vaginal rings may be advantageous because they are more discreet than oral products. The disadvantages of dapivirine vaginal rings are relatively low efficacy in clinical trials, likely not achieving multicompartment protection, and a low barrier to resistance of dapivirine. Open-label extensions of these trials are ongoing, and suggest a 50% reduction in HIV incidence compared to a counterfactual background HIV incidence rate [57, 58]. The dapivirine ring is currently under review by regulatory agencies; novel ring designs with both dapivirine and alternative agent active products are in development, including multi-purpose rings that couple anti-HIV, anti-STD, and/or contraceptive agents into a single ring formulation [59, 60].

## Vaginal Films

Vaginal films are dissolvable strips that are inserted into the vagina at least 15 min before intercourse and slowly release an antiviral substance. An in vitro study of a dapivirine film showed that more than half of dapivirine was released within the first 10 min of application [61]. Animal studies have administered various intravaginal films to mice [62, 63] and pigs [62] and were found to be safe without apparent histological changes.

In a phase 1 trial that assessed dapivirine film compared to dapivirine gel, placebo gel, or placebo film, both active agents were protective against HIV in ex vivo challenge assays [64]. Approximately 80% of the film users, compared with 68% of the gel users, reported that they would use the product in the future if it were found to be protective against HIV. In a two-arm, single-dose, crossover study of dapivirine gel and dapivirine film groups, both film and gel demonstrated reduced cervical tissue infectivity after ex vivo HIV challenge [65]. Similar results were seen for tenofovir film in both studies of daily dosing over a week as well as single-dose administration [66, 67].

Advantages for these films include their discreet use and quick dissolvability. In comparison to gels, films have additional advantages in that they have a reduced tendency to leak and, by virtue of their smaller volume, would be anticipated to be less disruptive to endogenous immune function in the vaginal compartment [64]. The disadvantages for these films include more difficult insertion when compared to gels and the lack of systematic concentrations. An additional phase 1 randomized trial is planned to evaluate the safety, acceptability, and length of time to dissolution of a placebo vaginal film among women.

## Microneedles/Microarray Patches

Microneedles (also known as microarray patches) are synthetic material devices applied to the skin that deliver drug nanosuspensions trans dermally through numerous projections [68]. Microneedles have been used to successfully deliver vaccine products, demonstrating immunogenicity for the influenza vaccine comparable to when administered via IM injection [69]. Only one pre-clinical study has evaluated microneedles for ARV delivery [70].

The advantages to microneedles over injectable agents include the avoidance of needle-stick injuries, no requirement for skilled medical personnel to administer the dose, potential for at-home use, and no need for specialized disposal [68]. In addition, although the product has an extended release mechanism, it can still be removed quickly if there is an adverse event. Disadvantages include a large patch size as volume of medication increases and issues in scale-up of microneedle production. A microneedle patch with rilpivirine is under investigation [70].

## Subdermal Implants

Subdermal implants, similar to currently available contraceptive implants, are porous polymer rods placed under the skin that provide a sustained release of an agent over a prolonged time interval. Three animal models evaluated either tenofovir alafenamide (TAF) or TAF and elvitegravir (EVG) and showed antiviral agents could be systemically delivered by this mechanism [71–73].

The advantage of implants is that they can be removed in the event of toxicity. Since the antiviral agent itself would be anticipated to have a short half-life, the liability of a prolonged PK tail would be avoided. The disadvantage is that implants have had varying degrees of acceptability, varying widely by geography and population. Human trials of HIV prevention agents delivered by implant are anticipated to begin in the near future.

## Broadly Neutralizing HIV-1 Monoclonal Antibodies

Broadly neutralizing HIV-1 monoclonal antibodies (bNAbs) are human or humanized antibodies derived or modified from HIV-infected individuals who were observed to have unusually delayed or arrested HIV progression. bNAbs appear to bind conserved regions of the HIV virion. The portfolio of bNAbs is rapidly expanding and currently includes antibodies against four major sites on HIV: CD4, N332, V1V2, and gp41 MPER. The current generation of bNAbs entering clinical trials has been molecularly engineered to improve breadth, specificity, and pharmacokinetics.

bNabs have been shown to successfully protect macaques against repeated SHIV challenges [74–76] and mice against intravenous challenges [77]. Three phase 1 studies reported that the VRC01 or VRC01LS administered either subcutaneously or intravenously were well tolerated [78–80]. Two phase 2b studies are currently ongoing to examine the efficacy of VRC01 with the first study among men and transgender persons who have sex with men in North America, South America, and Europe and the second study among women in sub-Saharan Africa. In addition, a number of first-in-human studies of single and combinations of

bNAbs as well as poly-functional bNAbs are in various stages of planning.

The advantages of bNAbs are their potential for long-acting HIV protection with infrequent dosing, their relative safety in early phase trials, and if successful, their preventive efficacy to inform potential vaccine design. The disadvantages of bNAbs include the need for parenteral administration, manufacturing complexities, costs, a small safety database to-date, and that anti-drug antibodies may be generated.

### Other Formulations and Modalities

Additional delivery systems for PrEP agents are also being investigated. Studies are currently evaluating electrospun fibers [81–86], enemas [87, 88], mucoadhesive intravaginal tablets [89], thin-film polymer devices [90], vaginal foams, and vaginal sponges. Small early-phase studies of PK and tolerability are encouraging, but little additional data are available.

## Conclusion

As the standard of care for HIV prevention improves, the pathway to regulatory approval of new HIV prevention products becomes fraught. It becomes increasingly complicated to assess the superiority or non-inferiority of new PrEP modalities when compared to control groups that have active comparators. For example, it is more difficult to discern the true efficacy of a new PrEP modality when the control arm allows for daily PrEP or on-demand PrEP. Novel trial design strategies, including counterfactual analyses that try to estimate hypothetical untreated/placebo incidence in the same or a similar population, will be paramount to the feasibility of studying new interventions. However, designs that are statistically sound, adaptive, and creative have yet to be accepted by regulatory agencies. It is important that there be widespread collaboration on such initiatives so as to ensure that promising prevention agents are evaluated quickly, and if appropriate, facilitated through regulatory and local approvals, implemented and scaled up as quickly as possible such that individuals who are at the most risk for HIV may benefit.

Research on new modalities of PrEP must integrate biomedical research and behavioral research to support conceptualization of processes required to move from awareness about the availability and efficacy of new PrEP formulations to uptake and persistence of these formulations. While long acting formulations of PrEP stand to address some of these issues, decision-making about whether to use these new PrEP modalities will depend on individual-level, interpersonal-level, community-level, and structural-level factors that must be considered in future research.

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### Compliance with Ethics Guidelines

**Conflict of Interest** Matthew R. Beymer, Ian W. Holloway and Craig Pulsipher declare that they have no conflict of interest.

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