Prevention of HIV for persons with low-frequency, high-risk exposures: PrEP (preexposure prophylaxis), PEP (postexposure prophylaxis), or 'PIP' (postexposure prophylaxis in-pocket)

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AIDS 2020, **34**:481–482

The optimal biomedical HIV prevention approach for individuals with infrequent high-risk exposures remains unclear. Daily preexposure prophylaxis (PrEP), while highly effective for HIV prevention for at-risk individuals [1], may incur excess cost, pill burden, and toxicity risk when exposures occur sporadically. So, what other options exist, and what is 'PIP?'

MSM who infrequently engage in condomless sex may consider on-demand PrEP (not advised for other risk groups because the principal study only enrolled MSM) [2]. However, this PrEP strategy, also known as intermittent, event-driven, or pericoital PrEP, or simply '2–1–1' because of the dosing protocol, remains controversial. Although 2–1–1 appeared effective when compared with placebo in a randomized trial, enrollees took a median 15 PrEP tablets per month and reported a median 8–10 sexual encounters per month [2]. In a substudy restricted to time periods in which enrollees reported taking fewer than 15 pills per month, participants reported sexual intercourse a median of 5 times per month [3]. Is this sufficient evidence to support 2–1–1 for MSM with less frequent exposures? That question stirs debate and some guidelines endorse the 2–1–1 option for MSM whereas others advise against it [4–6]. Furthermore, although some MSM report they often anticipate sexual encounters, indicating sufficient time to take PrEP prior to sex, many do not. Thus, this modality may be appropriate for some, but not all.

Postexposure prophylaxis (PEP) could be prescribed after each high-risk exposure and represents the conventional strategy when risk events are uncommon. However, this often requires a visit to the emergency department to obtain a starter pack of antiretrovirals (ARVs) for PEP, then referral to a clinic for follow-up and prescription of the remaining course. As has been documented and as any provider who offers outpatient PEP visits can attest to, significant attrition occurs between the emergency department and clinic follow-up, and these requirements present a barrier to PEP adherence [7]. Anecdotally, for MSM with low-frequency exposures, some clinicians prescribe ARVs to be taken 7 days prior to an expected exposure then 28 days after, but this is based only on predicted time to maximum concentrations of tenofovir diphosphate in rectal tissue and extrapolations from PEP data.

In this edition of *AIDS*, investigators from Toronto, Canada, present a novel twist to the traditional PEP model. A creative strategy, which they term 'PIP' for 'PEP in-pocket', may reduce some burdens and promote adherence. The authors describe a protocol in which carefully selected individuals with potential HIV exposures zero to four times per year (most were MSM reporting sexual exposures) received prescriptions for full 28-day courses of three-drug PEP, to be filled and kept on-hand then self-initiated immediately following a potential HIV exposure. Although an overall small study

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Received: 7 November 2019; accepted: 11 November 2019.

DOI:10.1097/QAD.0000000000002446

ISSN 0269-9370

($n = 79$ participants, of whom 21 self-administered a total 32 courses of PIP), the investigators report promising results. Notably, all 21 participants who self-initiated PIP reported starting the medications within 72 h of sex, all reported excellent adherence, and only one self-initiation instance was deemed inappropriate (prophylaxis probably unnecessary).

One can envision advantages of the PIP model. Importantly, it eliminates the onerous step of an emergency department visit. Prescribing PEP for self-initiation also allows time to identify and tackle insurance or cost issues prior to an exposure, instead of immediately after, when time is often pressing. Moreover, PIP may empower individuals to take greater control over their HIV prevention efforts and encourage awareness of risk. All in all, PIP appears to be a reasonable option for certain MSM with low-frequency, high-risk exposures, especially if they tend not to anticipate sexual encounters.

There may also be pitfalls to this strategy. For example, the protocol, at least as studied, still requires a visit in clinic after initiation of at-home PEP (adherence to this in the study was remarkably high, but this may be a hurdle for some individuals). In addition, diversion or misuse of the prescribed ARVs may occur; while this did not happen in the trial, it has been described (albeit uncommonly) in the literature [8].

Despite minor concerns, proof-of-concept studies of outside-the-box interventions like PIP are welcome and should be encouraged. If replicated for other at-risk demographic groups and in larger, prospective trials, dissemination of PIP could help to individualize biomedical HIV prevention strategies and boost the number of individuals accessing them. Hopefully, further studies can better define the optimal candidates for various prevention options, including PIP. It is noteworthy that in the current study, it was relatively common for a participant to switch from PIP to PrEP if high-risk encounters became more frequent, and a fair proportion had a history of PrEP use prior to PIP; the authors make the crucial point that HIV risk fluctuates and clinicians should regularly reassess the optimal method for each individual.

Future investigations could examine complementary approaches to further reduce barriers to PIP, such as telemedicine or other electronic health approaches that eliminate the requirement for any clinic visit. For example, many apps, websites, and telehealth programs now offer PrEP initiation and follow-up without an in-person appointment [9]. Self-administered HIV, sexually transmitted infection, and other tests, which are being explored as part of PrEP and other protocols, could be incorporated into PIP follow-up to promote quality care while reducing in-clinic requirements [10]. For now, HIV prevention options for persons with infrequent high-risk exposures (particularly for MSM given that multiple approaches have been studied) should be individualized.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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