**Viewpoint: Enabling timely HIV post-exposure prophylaxis (PEP) access in sub-Saharan Africa**

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Post exposure prophylaxis (PEP) is a World Health Organisation-endorsed, approach to prevent HIV acquisition from a recent sexual exposure by initiating an antiretroviral drug regimen, within 72 hours after the exposure, but ideally within 24 hours, and continuing for 28 days (1). Non-human primate studies suggest that PEP may reduce the risk of acquiring HIV by around 90% (2), with the efficacy likely to be higher the earlier PEP is initiated after a potential high risk sexual exposure. The current recommended regimen for PEP includes TLD (tenofovir/lamivudine/dolutegravir), the same as the recommended first line regimen for treatment of people with HIV. Most countries have policies to provide PEP, but these usually require a clinic visit and in practice use of PEP to prevent HIV due to a recent condomless sex exposure is extremely low. We hypothesize that removing barriers and providing easy, local PEP access would have a beneficial effect on HIV incidence which out-weighs any harms.

Our proposal is to consider making PEP (in the form of TLD) widely and freely available without prescription, along with a step change in levels of community education about all aspects of HIV to increase knowledge, limit stigma, increase awareness of PEP and thereby increase population-level motivation to access it when needed.    Wherever we distribute free condoms (e.g. free from vending machines, toilets, in public places, pharmacies, shops, bars, workplaces, and through peer outreach workers) we would have 28-day packs of TLD PEP available. The aim would be to ensure that everyone has the potential to access PEP within at most 24 hours of a sexual HIV risk. While adolescent girls and young women are a group for which it is particularly important to support access, there would be no intent to restrict access by age or gender. Oral contraceptives and post-coital contraception for women would ideally be distributed through the same mechanisms.

Such an approach would require community ownership and community-led education, with sophisticated education resources that explain potential benefits and possible risks and harms, allowing community members to be able to make informed choices. This approach is not intended as a replacement for existing in-person clinic services, but rather a complement to those services. PEP users who have self-accessed PEP would be advised to access online advice counsellors or visit a clinic or a pharmacist who is supporting PEP users. This in person contact would be to provide advice over HIV testing and monitoring for any adverse effects, and would also be important for providing contraception services and help for survivors of sexual assault. The message would in essence be as follows: “Condom use is the most effective means of prevention of transmission of sexual infections. If any sex that you have with is not protected from HIV risk by a condom or by you taking HIV pre-exposure prophylaxis (PrEP), make sure it is protected by starting TLD PEP within 24 hours, unless you know the partner not to have HIV or to have HIV viral suppression. You should continue PEP for a full 28 days. You may want to consider taking TLD PEP continuously afterwards so you are prepared if you have (another) risk, or you may wish to enrol for PrEP.  You are strongly advised to make use of our online counsellors or visit a clinic or a pharmacy to get advice, but if you cannot do this within 24 hours of your sexual risk start PEP in any case and then seek advice thereafter. This will include advice on HIV testing. It is important to have an HIV test to check that you did not already have HIV at the time of the sexual exposure – a negative test result while taking PEP does not mean you did not acquire HIV as a result of the exposure. You will not know if you got HIV from this exposure until a test at about 12 weeks after”

Several countries have policies to provide PrEP consisting of tenofovir/FTC to people at “substantial risk” of HIV. This is provided by the health care system and requires an HIV test before initiation. It can be difficult for some people to recognise or predict their risk and, if they do, to negotiate the process of accessing PrEP, which may involve disclosing sexual experiences. Use of PrEP has generally been fairly low thus far, particularly persistence of use (3, 4). The reasons for the lack of persistence of use include unpredictable nature of risk, pill size, concern over side effects as well as inability to attend clinic on a routine basis to receive an HIV test and renewed PrEP drug supply (e.g. 5). If the proposed PEP approach is implemented, this would raise the question of whether existing PrEP services (based on TDF/FTC) might adapt to also offer continuous TLD PEP as an additional PrEP option for people with recurrent sexual exposures over time. It would be an option to use TLD as PrEP since it contains drugs shown to be effective as PrEP. If drugs for HIV prevention are to be widely available as we describe the critical advantage of TLD compared with tenofovir/FTC PrEP is that drug resistance risk is much lower when a person with HIV takes the drugs (6, 7). Increasing access to PEP could provide a relatively safe bridge to tenofovir/FTC PrEP for many individuals who might not consider themselves high risk until a sexual exposure occurs.

Encouraging use of TLD for prevention presents challenges for HIV testing. Should dolutegravir be added to a PrEP regimen of tenofovir/FTC, the viral load of a person who becomes infected with HIV may be so low that antibody levels are insufficient for 3rd generation HIV tests to be positive (as has been seen in some cases with cabotegravir used as PrEP (8)).

The primary potential benefit of this approach is that it provides a realistic means for people to protect themselves from HIV when a sexual risk was unanticipated and it was not possible for them to use a condom. However, we hypothesize that wide TLD availability would also be of benefit people with HIV who have difficulty accessing care, and could decrease late presentation with advanced HIV disease. It would give the opportunity for people with HIV who run out of drug to have access to an emergency supply to tide them over. It could also lead to some people who suspect they may have HIV, but are afraid to test for it (e.g. 9), to take TLD to treat their HIV while avoiding the real or perceived stigma they fear with engaging with health care, which could be of net benefit, particularly if this leads them subsequently to engage in care.

Alongside these potential benefits there are concerns and possible harms with the approach which would need to be considered during any implementation. This approach could have the effect of reducing engagement with clinical services, including sexual and reproductive health services. Further, while dolutegravir is generally a safe drug, any additional adverse effects due to dolutegravir might be considered unnecessary if TLD is used as PrEP. Dolutegravir has been associated with some neuro-psychiatric toxicity and very rare serious toxicity (hypersensitivity, liver toxicity) and is suspected of leading to weight gain in some people (7). It is possible there is a very small increased risk of neural tube defects in babies of women becoming pregnant while taking dolutegravir (10). That said, cabotegravir, has been approved for use in HIV negative people as PrEP (11, 12). There would also be a risk that some people with HIV who have been under care may default from that care as they know they can access their antiretroviral drugs locally and easily; thus they would be unmonitored. Lastly, if the approach is introduced in one area and not others there is the possibility of a black market for drugs arising.

We hypothesize that the benefits of the approach would outweigh the risks and harms, but its impact and cost-effectiveness should be studied. Net benefits are most likely in settings where the population prevalence of unsuppressed HIV is highest. One way to study the effect of the approach would be to select one or more relatively self-contained communities with high HIV incidence and with an inclusive community leadership who are motivated to pilot the approach. A random sample survey would be conducted at baseline (along the lines of the PHIA surveys) (13). The approach would then be introduced. Active surveillance for incidence of drug toxicity. There would follow a second independent (i.e. a new sample) random sample survey after a period of time to study differences from baseline in PEP, PrEP and ART use, viral suppression levels, HIV diagnosis coverage, and other key measures. Any evaluation would need to be accompanied by extensive process evaluation work to monitor acceptability, accessibility, feasibility and unintended consequences of the programme.

The nature of PEP means that to be useful it must be very easily and locally available. We propose an approach to enable this.

**Competing Interests**

Authors declare no conflicts of interest.

**Author Contributions**

AP wrote the first draft. All authors contributed with ideas and suggestions.

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**References**

1. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. <https://www.who.int/publications/i/item/9789240031593>
2. Irvine C, Egan KJ, Shubber Z, Van Rompay KK, Beanland RL, Ford N. Efficacy of HIV Postexposure Prophylaxis: Systematic Review and Meta-analysis of Nonhuman Primate Studies. Clin Infect Dis. 2015 Jun 1;60 Suppl 3:S165-9. doi: 10.1093/cid/civ069. PMID: 25972498.
3. Stankevitz, Kayla; Grant, Hannah; Lloyd, Josie; Gomez, Gabriela B; Kripke, Katharine; Torjesen, Kristine; Ong, Jason J; [Terris-Prestholt, Fern](https://researchonline.lshtm.ac.uk/view/creators/phpufter.html); (2020) [Oral preexposure prophylaxis continuation, measurement and reporting.](https://researchonline.lshtm.ac.uk/id/eprint/4656994/) AIDS, 34 (12). pp. 1801-1811. ISSN 0269-9370 DOI: <https://doi.org/10.1097/QAD.0000000000002598>
4. Heffron R, Ngure K, Odoyo J et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa [version 2; peer review: 2 approved] Gates Open Research 2018, 1:3 <https://doi.org/10.12688/gatesopenres.12752.2>
5. Muhumuza R, Sentoogo Ssemata A, Kakande A, Ahmed N, Atujuna M, Nomvuyo M et al. Exploring Perceived Barriers and Facilitators of PrEP Uptake among Young People in Uganda, Zimbabwe, and South Africa. Archives of Sexual Behavior (2021) 50:1729–1742
6. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G et al. Risk of Drug Resistance Among Persons Acquiring HIV Within a Randomized Clinical Trial of Single- or Dual-Agent Preexposure Prophylaxis. J Infect Dis 2015; 211, 8, 15: 1211–1218. <https://doi.org/10.1093/infdis/jiu677>
7. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med 2019; 381: 803–15. <https://doi.org/10.1007/s10508-020-01880-y>
8. <https://www.nature.com/articles/d41586-021-00618-7>
9. Kazuma-Matululu Thokozani, Nyondo-Mipando Alinane Linda. “Men Are Scared That Others Will Know and Will Discriminate Against Them So They Would Rather Not Start Treatment.” Perceptions of Heterosexual Men on HIV-Related Stigma in HIV Services in Blantyre, Malawi. Journal of the International Association of Providers of AIDS Care, 20: 1-10 DOI: 10.1177/23259582211059921
10. Zash R et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana. AIDS 2020 virtual. 6–10 July 2020. Oral late breaker abstract OAXLB0102. <https://cattendee.abstractsonline.com/meeting/9289/presentation/3500>
11. Delany-Moretlwe S et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: interim results from HPTN 084. HIV Research for Prevention (HIVR4P) virtual conference, abstract HY01.02, 2021.
12. ([https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention](https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.fda.gov%2Fnews-events%2Fpress-announcements%2Ffda-approves-first-injectable-treatment-hiv-pre-exposure-prevention&data=04%7C01%7Candrew.phillips%40ucl.ac.uk%7C455a6df10f8a4a51585608d9c4067517%7C1faf88fea9984c5b93c9210a11d9a5c2%7C0%7C0%7C637756355134402904%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C2000&sdata=fvdN3YAj2jXYUn9Iy3j6dxDUsSFS4mtCD1GJdn5vyss%3D&reserved=0).
13. PHIA <https://phia.icap.columbia.edu/>