Commentary

Taking the daily grind out of HIV prevention

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Despite the proven efficacy of daily oral PrEP (pre-exposure prophylaxis against HIV infection) in high-risk populations – like men who have sex with men (MSM), injecting drug users, serodiscordant couples, and sex workers – adherence and continuation rates decline over time, thereby reducing PrEP’s public health impact [1].

Contributing to this decline, and to low levels of PrEP initiation, are the burden and stigma associated with taking a daily PrEP pill [2] or, for MSM only, a 2+1+1 on-demand oral regimen [3].

Given the challenges associated with the current PrEP options, there is an urgent need to develop new user-friendly PrEP or PEP (post-exposure prophylaxis against HIV infection) dosage forms and dosing regimens.

To that end, a study recently published in EBioMedicine by Massud and coworkers describes willingness to use a single-dose PrEP or PEP regimen among MSM and the biological efficacy of a triple combination of HIV inhibitors in a macaque HIV infection model [4].

The source for the willingness to use data was a 2017 online survey among sexually active MSM in the United States. A significant percentage of survey participants were willing to consider using a single-dose PrEP or PEP regimen. PrEP was clearly preferred over PEP. Among all survey respondents, willingness to use was highest (83.4%) for PrEP 24 h after sex, and lowest (67.1%) for PrEP 24 h before sex. Participants not currently taking PrEP preferred a single-dose PrEP/PEP regimen compared to daily PrEP, and PrEP users were less willing to use a single-dose PrEP 24 h before sex than participants who were not using PrEP. These differences could reflect different sex practices between the two groups and/or an increased awareness of the challenges involved in taking daily oral PrEP.

The authors also determined the pharmacokinetics (PK) of a prototype single-dose PrEP or PEP dosage form in human and macaque plasma, PBMCs (peripheral blood mononuclear cells), and rectal tissues. It contained the reverse transcriptase inhibitors emtricitabine (FTC) and tenofovir alafenamide (TAF), the integrase inhibitor elvitegravir (EVG), and the pharmacoenhancer cobicistat. FTC and TAF are in Descovy®, which is approved for PrEP use in HIV-negative men and adolescent boys, excluding individuals at-risk from receptive vaginal sex. All four drugs are in the approved HIV treatment Genvoya®. The addition of EVG, which the authors had previously shown penetrates and concentrates in rectal tissues, potentially extends the window of intervention achieved with FTC/TAF alone, since integration of viral DNA into the host genome occurs several hours after reverse transcription.

Having demonstrated favorable PK for FTC, TAF, and EVG in humans and macaques, the authors evaluated the biological efficacy of the prototype product in a validated macaque rectal simian HIV (SHIV) infection model. Efficacy estimates for a single oral dose of the combination product dosed 4 h before or 2 h after rectal SHIV exposure were 92% and 100% respectively. These data are comparable to the efficacy data for FTC/TAF and FTC/TDF in MSM. Efficacy estimates for a dose given 6 h or 24 h after SHIV exposure were 80% and 65%, respectively, whereas the efficacy estimate for a two-dose regimen given at 24 h and 48 h post virus exposure was 77%. The 24 h/48 h data underscore the importance of EVG in the formulation, since administration of FTC and tenofovir at 24 h and 48 h after virus exposure failed to protect macaques in the SHIV rectal challenge model [3]. One limitation of the macaque study is that variances in the efficacy estimates in some regimens were large due to the small sample sizes.

The data presented by Massud et al. support the notion that a combination product containing two different classes of HIV inhibitor could represent an effective and perhaps more acceptable product to prevent rectal HIV infection. Additional studies will be needed to determine if the combination product also protects vaginal or penile tissues. Preclinical and clinical studies on a range of combination products will be needed to identify the best candidate to advance and answer a key question: will a modified dosing regimen increase PrEP/PEP uptake, adherence, and continuation rates enough to see a meaningful public health impact?

In the meantime, any PrEP development candidate will be compared to what could be the next PrEP product for females and males to receive regulatory approval: CAB-LA [5].

CAB-LA is an injectable, long acting (2 months between injections) formulation of the HIV integrase inhibitor cabotegravir. Recently disclosed findings from HPTN 083, a Phase 2b/3 study of cisgender men and transgender women who have sex with men, showed a 66% reduction in incident HIV infections in study participants given CAB compared to FTC/TDF. A companion study, HPTN 084, is underway in
cisgender women. If approved, CAB-LA will be the first long-acting dosage form approved for HIV PrEP for females and males and could offer a more acceptable option to daily pills for some people.

**Declaration of Interests**

The author declares no conflicts of interest.

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