PrEP patterns matter

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The HIV prevention toolbox has recently included a new item: the use of antiretroviral drugs that act by blocking viral replication at the time of viral entry, therefore inhibiting the establishment of infection. The approach has been called pre-exposure prophylaxis (PrEP) and the current drug combination mainly targets HIV reverse transcriptase. Several clinical trials have been run to test the efficacy of such strategy, targeting different high-risk populations, and the results have been variable. In some instances, such as in the recently concluded Partners’ PrEP study, up to 75% fewer infections occurred in the drug arm as compared to the placebo. Some studies showed lower protection and some were stopped for futility at interim analyses. These negative results have been mostly attributed to low adherence. In fact, plasma levels of the drugs revealed the adherence to be much lower that what was estimated based on the self-reported adherence by the study participants.

Aside from adherence though, other variables could modify the efficacy, such as pharmacokinetic characteristics as well as drug-taking patterns. PrEP patients may skip doses periodically, randomly or in large blocks. In some cases, they may adjust their pill taking patterns in correspondence to their expectations to have sex (risk-driven patterns).

Dr. Dobromir Dimitrov, a Senior Staff Scientist in the Vaccine and Infectious Disease Division at Fred Hutch, decided to approach the possible effects of such variables by modeling the influence of different pill-taking patterns and of waning of drug concentration on instantaneous PrEP efficacy. Behavioral and epidemiological assumptions were made based on published research on sexual behavior and HIV transmission in South Africa. The model shows that pill-taking patterns affect

Observed PrEP efficacy under different PrEP protection profiles and pill-taking patterns. Box plots (5th, 25th, 50th, 75th, and 95th percentiles) reflect estimated variation over 100 trials simulated. Common 50% adherence is assumed under first 3 scenarios. Risk-driven scenarios, assuming that PrEP is more likely to be taken when sex is expected, result in 29% and 37% actual adherence.

Figure provided by Dr. Dobromir Dimitrov
protection differently when short-lasting and long-lasting effects of the drug are assumed. In fact, if PrEP is assumed to maintain some level of protection for over five days, the number of days lacking protection is more limited when the drug is taken periodically as compared to block adherence (where the drug-taking is interrupted for longer stretches of time).

Given these observations, the spread of results observed in clinical trials is possibly due to a combination of factors. For instance, the high protection observed in the Partners’ PrEP study is likely the result of high adherence with limited block-pill taking pattern, with the long-lasting effect of the orally administered drugs. Moderate efficacy could be explained with medium (50%) adherence under periodic pill taking with intermediate protection or under random pill taking with long protection. Topical application of PrEP is modeled by short protection and observes up to 40% efficacy, similar to the study CAPRISA 004 with high adherence or risk-driven pill taking. A combination of low adherence, block pill-taking, and short lasting protection might result in lack of efficacy of the drug.

The question about protection, provided by PrEP, is very complex and calls for a careful design of clinical studies or drug implementation. Basically, it is important to identify the behavioral patterns of the population, and try to direct the use of PrEP based on what a subject can sustain in the short and long term. Many factors can influence PrEP use, such as perceived or real HIV exposure, economical factors, access to providers, support from the partner, family and society. All of them can influence adherence and pill-taking patterns, and, as this paper shows, all of this matters for protection.

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