When Does an HIV Intervention Outperform the Placebo in a Community Setting?

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Many early generation HIV vaccines or pre-exposure prophylaxis (PrEP) candidates will probably only offer modest reductions in susceptibility to infection, even when an individual adheres perfectly to the specified booster schedule or guidelines for use. Given the complexities of human behavior and interactions within communities, a marginal PrEP or vaccine efficacy at the individual level can have unexpected consequences in HIV interventions at the community level. To optimize the design of community-level trials for testing HIV prevention approaches, Dr. Dobromir Dimitrov (Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center) mathematically modeled the population effectiveness of two different approaches for reducing the rate of HIV transmission. He did so in collaboration with Dr. Benoît Mâsse (CHU Sainte-Justine Research Centre, University of Montreal) and Dr. Marie-Claude Boily (Department of Infectious Disease Epidemiology, Imperial College London). In addition to highlighting the likely public health impacts of two simulated interventions, their results point to specific ways of improving the design of clinical trials for testing HIV prophylaxis drugs, which are just starting to be approved by the U.S. Food and Drug Administration (*e.g.*, Truvada®).

A drug company seeking licensure for a prophylaxis candidate or vaccine needs only to show that the product is statistically superior, even marginally so, to a matched placebo in a small number of individual-based clinical trials, often only one or two. In essence, this simply requires the company to demonstrate that the lower bound of the 95% confidence interval around the estimated efficacy is greater than 0%. However, a product with an efficacy that is low but statistically significant can actually have a negative impact on the HIV epidemic at the community level (Boily *et al.*, 2008). This can result from imperfect adherence to an intervention regimen, or from an increase in risky sexual behavior due to higher-than-actual perceived efficacy. To offset such effects, epidemiologists will often only consider a clinical trial to be successful if the results surpass a minimum individual-level efficacy (MIE) set substantially higher than 0% (Boily *et al.*, 2008). The tradeoff is that, as researchers nudge the MIE set-point higher and higher, the size of the trial grows exponentially in terms of the number of participants needed and cost.

Dimitrov *et al.* adapted their modeling approach from an earlier simulation study of the effects of antiretroviral-based vaginal microbicides (VBM) in developing countries (Dimitrov *et al.*, 2010). In the more recent modeling study, the authors investigated how the precision of the efficacy estimate obtained in clinical trials with different MIE set-points affects the projected public-health impact of antiretroviral-based oral PrEP and VBM. They did so under a variety of model conditions, including: intervention scenarios differing in degree of population coverage, rate at which antiretroviral resistance develops and level of adherence; varying levels of actual product efficacy; and either uni- or bi-directional protection. Uni-directional interventions were assumed to reduce only the user's susceptibility to HIV, whereas bi-directional interventions were assumed to reduce the user's infectiousness as well as susceptibility. For each set of conditions, parameter values were sampled 10,000 times from researcher-defined intervals of interest, or from empirically-based distributions representative of sub-Saharan Africa. This yielded outcome distributions for the authors' main public health endpoint, fraction of HIV infections prevented over ten years (see figure).

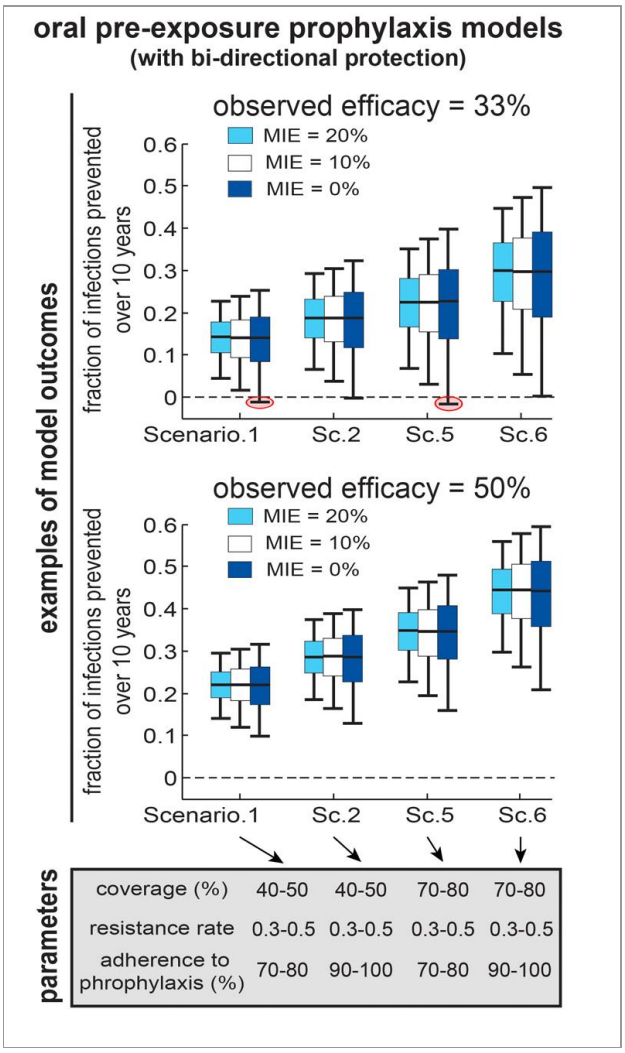
In their simulations, Dimitrov *et al.* found that both PrEP and VBM were almost always beneficial across scenarios and parameter values. Overall, PrEP had a larger positive impact on the HIV epidemic than VBM, consistent with the latter intervention being used by women only and being restricted to a single route of transmission. Increasing the MIE set-point improved the precision of the public health endpoint for both interventions across all model conditions. This was expected, since a higher MIE requires the enrollment of more trial participants to achieve the same statistical power for a more stringent null hypothesis. Not surprisingly, a larger MIE also reduced the likelihood of interventions with a negative impact on the epidemic (red ovals in the figure). Despite these important effects of the MIE set-point on trial outcomes, the authors found that implementation factors and characteristics of the target communities (*i.e.*, the different intervention scenarios) were the most important drivers of uncertainty in predicting public health outcomes.

In light of the limitations in funding available for clinical trials of HIV intervention strategies, the findings of Dimitrov *et al.* have very significant implications. Often, the geometric increase in trial cost is not justified by the moderate improvement in endpoint precision that accompanies a linear increase in MIE. The authors recommend that funds may be better spent, in some cases, on a greater number of moderate-sized clinical trials. This would allow epidemiologists to investigate a greater diversity of intervention strategies while being more thorough about evaluating critical implementation factors and population characteristics during each trial.

Dimitrov DT, Mâsse BR, Boily MC. 2013. Beating the placebo in HIV prevention efficacy trials: the role of the minimal efficacy bound. *J. Acquir. Immune Defic. Syndr.* 62:95-101.

Also see: Boily MC, Abu-Raddad L, Desai K, Masse B, Self S, Anderson R. 2008. Measuring the public-health impact of candidate HIV vaccines as part of the licensing process. *Lancet Infect. Dis.* 8:200-07.

Dimitrov DT, Mâsse B, Boily MC. 2010. Who will benefit from a wide-scale introduction of vaginal microbicides in developing countries? *Statistical Communications in Infectious Diseases* 2: Issue 1, Article 4, doi:10.2202/1948-4690.1012.



Adapted from the manuscript

Modeled effects of oral pre-exposure prophylaxis (PrEP) on the cumulative fraction of HIV infections prevented over a ten year period (y-axes) under four intervention scenarios (x-axes). Observed 'actual' efficacies were set to 33% and 50% for the top and bottom plots, respectively. For each scenario, distribution ranges are given (below the plots) for three parameters: coverage (% individuals in the population receiving PrEP); resistance (annual rate at which antiretroviral drug resistance develops); and adherence (relative PrEP efficacy under imperfect adherence by an individual). In every scenario, the minimum desired individual-level efficacy (MIE) was set to 0%, 10% or 20%, as indicated by the color-coded keys. Red ovals highlight portions of the outcome distributions where the PrEP intervention scenario actually poses a slight risk of negative impact on the HIV epidemic.