Predicting effect of pre-exposure prophylaxis on HIV epidemics

We agree with Angela Kashuba and colleagues (June 30, p 2409) that it is essential to develop new methods for measuring adherence to pre-exposure prophylaxis (PrEP) for HIV prevention in clinical trials. However, another important issue also needs to be addressed. Specifically, how can adherence data from clinical trials be interpreted and used to predict the success of PrEP in reducing transmission in the real world? We suggest that one approach is to use mathematical models to translate these data into population-level predictions.

In each of the successful clinical trials of PrEP, several estimates of efficacy have been calculated: an overall estimate of efficacy calculated by use of data from all individuals irrespective of their level of adherence, and adherence-stratified efficacies for which each estimate was calculated for a specified range of adherence. For example, in the IPReX trial (in which adherence was defined on the basis of number of visits) the overall efficacy was estimated to be 42% and adherence-stratified efficacies (based on an as-treated analysis) were estimated to be 68% (adherence >90%), 34% (50–90% adherence), and 16% (<50% adherence). Such data are necessary, but—even if adherence is measured accurately—are not sufficient for predicting the success of PrEP in the real world. To make predictions, it is also necessary to know how population-level patterns of adherence to PrEP will affect success, where such patterns are defined in terms of the proportion of the population in each adherence category.

The figure shows predictions from a mathematical model that translates adherence data from clinical trials of PrEP into population-level predictions. Contours show the reduction in transmission as a function of the proportion of the population that is highly (>90%) adherent to PrEP (Y-axis) and the average adherence in the rest of the population (X-axis). To generate these predictions, adherence-stratified efficacy estimates, based on clinical trial data, were used. The figure illustrates that population-level adherence patterns (which cannot be measured in clinical trials) will be as important as efficacy in determining success. Therefore even when it becomes possible to measure adherence accurately in clinical trials, these trials will not be able to generate all of the necessary data for predicting the success of PrEP in reducing HIV transmission in the real world.

We declare that we have no conflicts of interest.

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Inheritance of coronary artery disease in men

In their intriguing study, Fadi Charchar and colleagues (March 10, p 915) suggest that one of the Y chromosome variants, haplogroup I, is associated with increased risk of coronary artery disease (CAD) in men. The study was substantially based on data from the WOSCOPS trial, which randomised 6595 statin-naive men, who had raised plasma cholesterol concentrations and no history of myocardial infarction, to receive 40 mg pravastatin (50% of men) or placebo daily. It is possible that paternal haplogroup I is associated with a poorer response to pravastatin, and thus a greater association with CAD, than are other haplogroups. If this were the case, the overall increased association with CAD noted in the WOSCOPS population (including both statin users and non-users) could have been the result of confounding or mediation by statin use associated with exposure, inheritance of paternal haplogroup I, and CAD outcome, rather than a direct association between haplogroup I itself and CAD.

Charchar and colleagues adjust their findings to 31 autosomal genetic variations that were previously associated with CAD. However, other autosomal genetic variations noted in the same WOSCOPS population were found to be significantly associated with differential response to pravastatin, thus affecting