L'inférence causale en présence de dépendance et de structure de réseau
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Estimating the protective effect of longitudinal drug concentration in pre-exposure prophylaxis for HIV prevention

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Pre-exposure prophylaxis (PrEP) using antiretroviral drugs for HIV prevention has been evaluated in multiple randomized trials. Though most trials have shown a benefit of PrEP, there is substantial variation in the effect estimates. Much uncertainty remains about the relationship between drug concentration in blood plasma and the reduction in HIV risk. Key challenges in estimating this relationship include the following: data on drug concentrations are relatively sparse and are collected via case-control or case-cohort sampling within the active treatment arm(s); adherence to assigned study drug may vary by study visit; and study visits may be missed and patients may be lost to follow up. To address these challenges, we apply targeted maximum likelihood estimation (TMLE) to estimate the protective effect of drug concentration against HIV infection using longitudinal data from two randomized, placebo-controlled clinical trials of daily PrEP: Partners PrEP and VOICE. In each, we compare HIV infection rates under two treatment regimes: plasma concentration of drug set to be always above (or always below) a given threshold at each visit over the first 18 months of the trial. Our estimates of the protective effect of high plasma concentrations of drug are similar to those from previous analyses of the Partners PrEP trial. In contrast, in the oral dosing arm of the VOICE trial our estimate of the protective effect is in the direction of benefit, unlike previous analyses; however, our corresponding confidence intervals are relatively wide and do not rule out the null hypothesis of no effect. Additionally, in the gel arm of the VOICE trial, we estimated a much higher protective effect of having quantifiable levels of tenovoir than previous analyses. In both trials, because plasma concentration measurements were relatively sparse and events (seroconversions) relatively rare, we were limited in the number of time-dependent confounders that could be adjusted for. *Coauthors: Claire Ruberman, Jon Arni Steingrimsson, Craig Hendrix.*

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