## Principal stratification on time-varying behaviors in HIV prevention trials

by

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## Abstract

In HIV prevention trials, it is frequently of interest to estimate the intervention effect that adjusts for posttreatment behavioral variables, such as treatment compliance and unprotected sex. For example in the recently completed HPTN 035 trial, there is differential condom-use between the three gel arms and the no-gel arm, so that ITT analyses yield the net treatment effect that includes the indirect effect mediated through the differential condom use. Various statistical methods in causal inference have been developed to adjust for posttreatment variables. In the context of HIV prevention trials, we argue that the principal stratification framework is more appropriate as it does not model the effect of intermediate behavioral variables on HIV infection. We extend principal stratification to time-varying behavioral variables in HIV prevention trials with a time-to-event endpoint. Using the HPTN 035 trial as an illustrative example, we formulated the causal estimands of interest, established assumptions that enable identifiability of causal estimands, and developed maximum likelihood methods for estimation. The novelty is to model the time- varying principal strata and the HIV outcome by a hidden Markov model (HMM), based on features of HIV prevention trials. Model diagnostics and sensitivity analyses are conducted to evaluate critical assumptions.