


Vaccine efficacy assessment under two-phase sampling based on the causal effects of stochastic interventions


Nima Hejazi


Thursday, 21 March 2019

Graduate Group in Biostatistics, and
Center for Computational Biology,
University of California, Berkeley

 nshejazi

 nhejazi

 nimahejazi.org

 bit.ly/2019_bstars_shift

joint work with David Benkeser and Mark van der Laan



The burden of HIV-1

- The HIV-1 epidemic — the facts:
 - now in its fourth decade,
 - 2.5 million new infections occurring annually worldwide,
 - new infections outpace patients starting antiretroviral therapy.
- *Most efficacious* preventive vaccine: 31% reduction rate.
- **Question:** How can HIV-1 vaccines be improved by modulating immunogenic CD4+ or CD8+ response profiles?

HVTN 505 trial examined new antibody boost vaccines

- HIV Vaccine Trials Network (HVTN) 505 vaccine efficacy RCT with $n = 2504$ (Hammer et al. 2013).
- Immunogenic response profile only available for second-stage sample of $n = 189$ (Janes et al. 2017).
- Two-phased sampling mechanism: 100% inclusion rate if HIV-1 positive in week 28; variable otherwise.
- **Question:** How would HIV-1 infection risk in week 28 have differed had immunogenic response (due to vaccine) differed?

- Baseline covariates (W): sex, age, BMI, behavioral HIV risk.
- Intervention(s) (A): post-vaccination T-cell activity markers.
- Outcome (Y): HIV-1 infection status at week 28 of trial.
- **Conclusion:** Understanding which immune responses impact vaccine efficacy helps develop more efficacious vaccines.
- A vaccine effective at preventing HIV-1 acquisition would be a cost-effective and durable approach to halting the worldwide epidemic.
- Identifying vaccine-induced immune-response biomarkers that predict a vaccine's ability to protect individuals from HIV-1 infection is a high priority.
- The study was halted on 22 April 2013 due to absence of vaccine efficacy. There was no significant effect of the vaccine on the primary infection endpoint of HIV-1 infection between week 28 and

Two-phase sampling censors the complete data structure

- Complete, unobserved data $X = (W, A, Y) \sim P_0^X \in \mathcal{M}_{NP}^X$, as per the full HVTN 505 RCT (Hammer et al. 2013):
 - W — baseline covariates: sex, age, BMI, behavioral HIV risk,
 - A — intervention: immune response profile for CD4 and CD8,
 - Y — outcome of interest: HIV-1 infection status by week 28.
- Observed data $O = (\Delta, \Delta X) = (W, \Delta, \Delta A, Y)$, $\Delta \in \{0, 1\}$, as per the second-stage sample of Janes et al. (2017).

- P_0^X — true (unknown) distribution of the full data X ,
- \mathcal{M}_{NP}^X — nonparametric statistical model.

Stochastic interventions define the causal effects of shifts

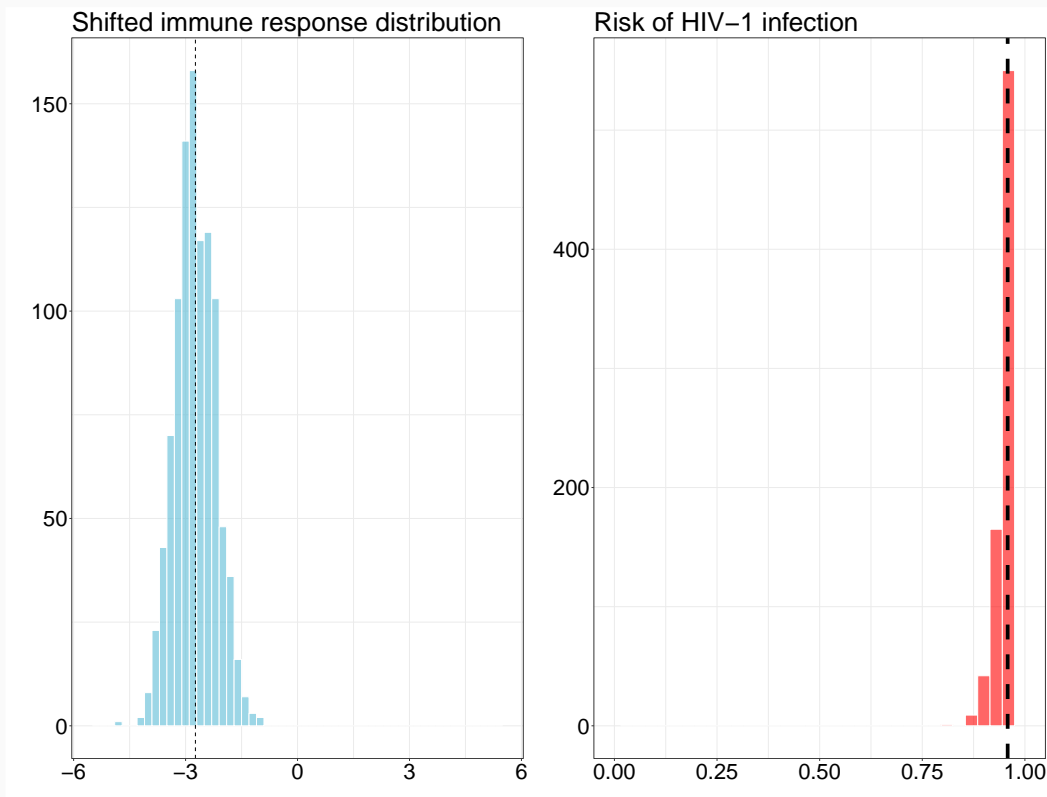
- Causal estimand: counterfactual mean of HIV-1 infection under a *shifted* immunogenic response distribution.
- Díaz and van der Laan (2012; 2018): *Shift* interventions?

$$d(a, w) = \begin{cases} a + \delta, & \text{if plausible} \\ a, & \text{otherwise} \end{cases}$$

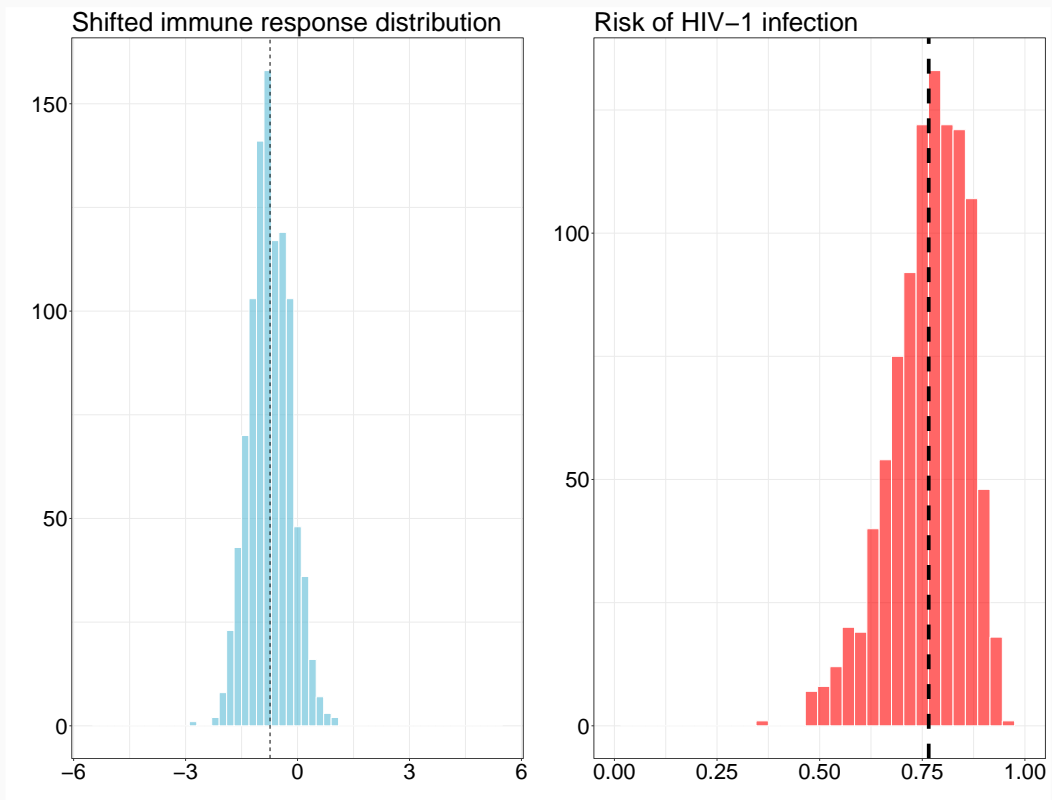
- Díaz and van der Laan (2012; 2018) give a statistical target parameter and influence function for the complete data case.
- **Challenge:** parameter estimation requires conditional density estimation. Nonparametric options?

- For HVTN 505, $\psi_{0,d}$ is the counterfactual risk of HIV-1 infection, had the observed value of the immune response been modified to originate from the distribution of the rule $d(A, W)$.
- Several different ways to consider stochastic interventions.
- Starts with Mark and Ivan's simple stochastic shift.
- Extensions to modified treatment policies.
- The new value of A may be denoted $A^* \sim G^*(\cdot | W)$, where $A^* = d(W, U^*)$ for a rule d and random error U^* .

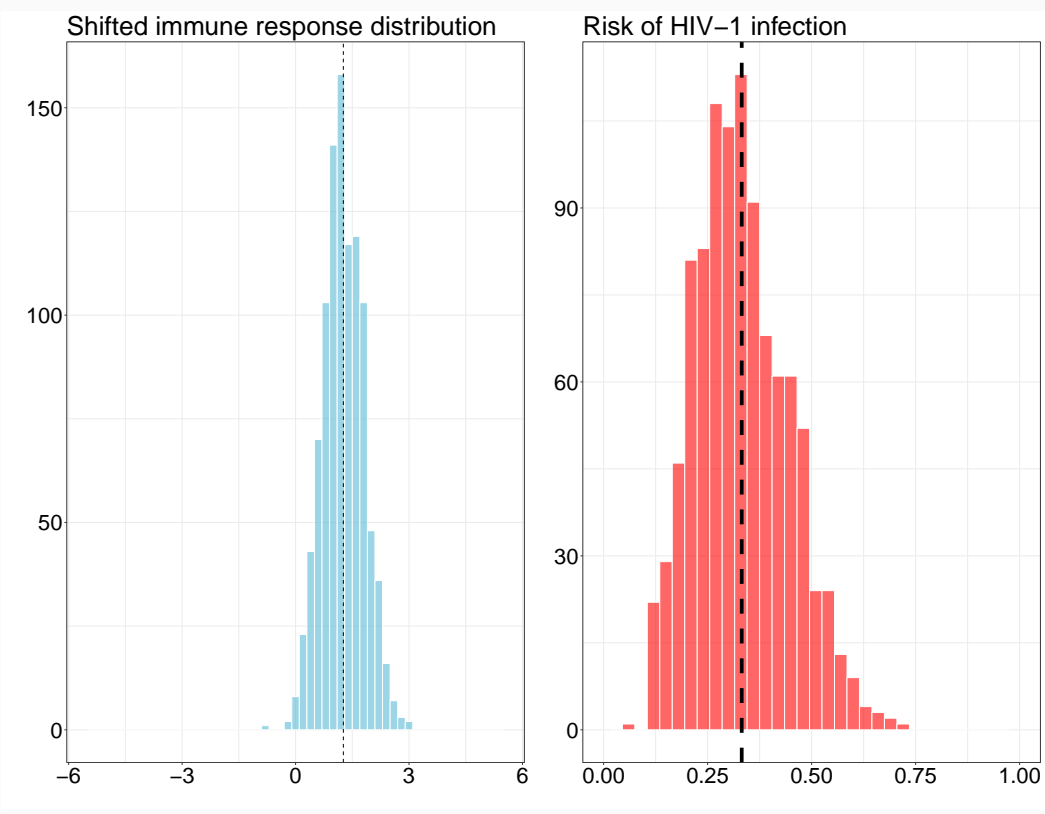
HIV-1 risk under stochastically shifted immune responses



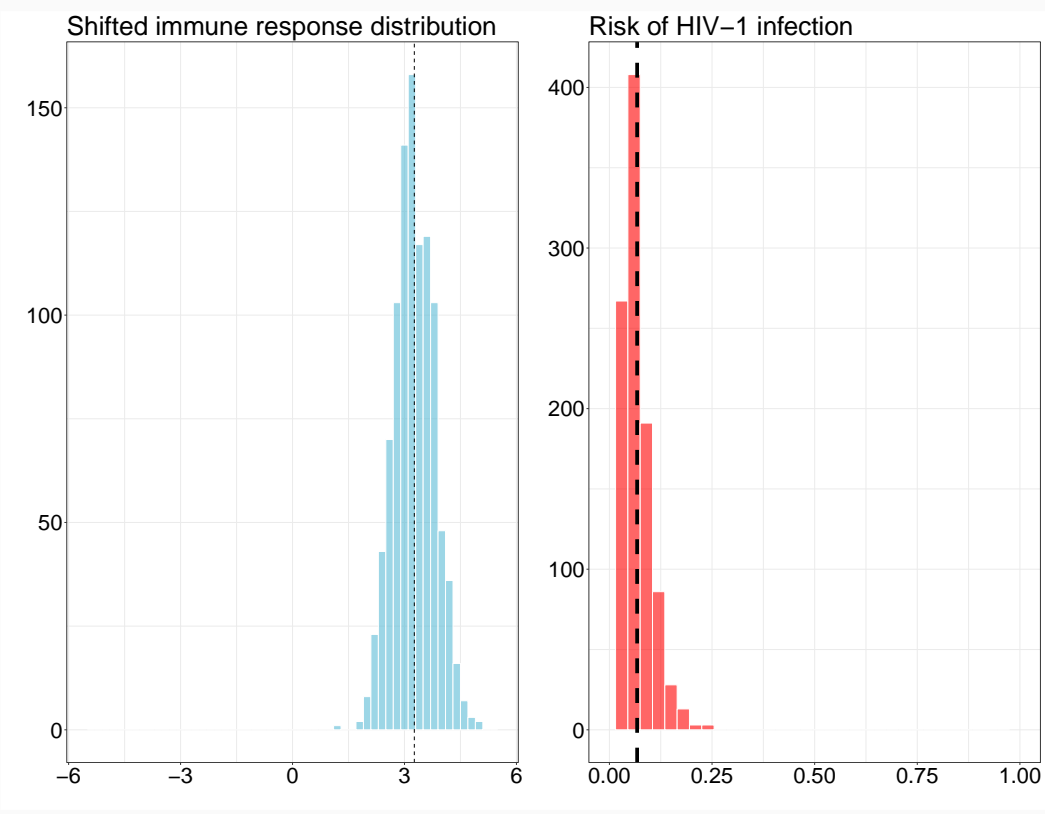
HIV-1 risk under stochastically shifted immune responses



HIV-1 risk under stochastically shifted immune responses



HIV-1 risk under stochastically shifted immune responses



Efficient estimators in spite of two-phase sampling

- What if sampling mechanism $\pi_0(Y, W) = \mathbb{P}(\Delta = 1 \mid Y, W)$ is not known by design? Nonparametric estimation of $\pi_0(Y, W)$?
- Building on Rose and van der Laan (2011), we provide
 - asymptotically linear and nonparametric-*efficient* estimators;
 - multiply *robust*, with 2 forms of double robustness;
 - Gaussian limiting distributions and Wald-type CIs.
- New open source software for deploying such estimators:
 - <https://github.com/nhejazi/haldensify> (densities)
 - <https://github.com/nhejazi/txshift> (AIPW, TMLE)
 - <https://github.com/tlverse/tmle3shift> (TMLE)

- **Asymptotic linearity:**

$$\Psi(P_n^*) - \Psi(P_0^X) = \frac{1}{n} \sum_{i=1}^n D(P_0^X)(X_i) + o_P\left(\frac{1}{\sqrt{n}}\right)$$

- **Gaussian limiting distribution:**

$$\sqrt{n}(\Psi(P_n^*) - \Psi(P_0^X)) \rightarrow N(0, \text{Var}(D(P_0^X)(X)))$$

- **Statistical inference:**

$$\text{Wald-type confidence interval : } \Psi(P_n^*) \pm z_\alpha \cdot \frac{\sigma_n}{\sqrt{n}},$$

where σ_n^2 is computed directly via $\sigma_n^2 = \frac{1}{n} \sum_{i=1}^n D^2(\cdot)(X_i)$.

How does this help in fighting the HIV-1 epidemic?

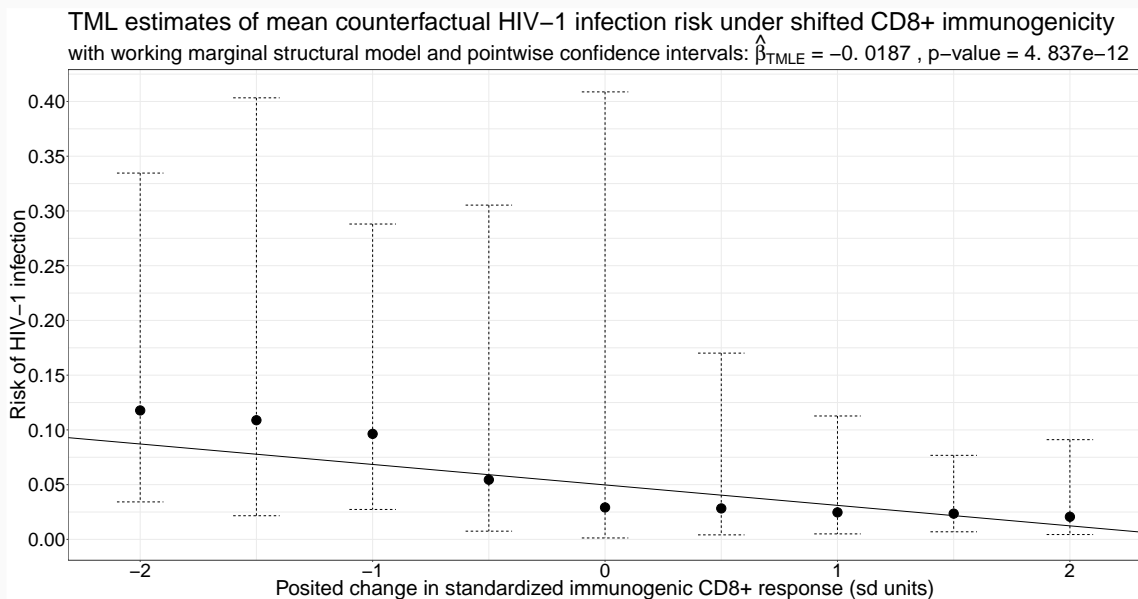


Figure 1: Analysis of HIV-1 risk as a function of CD8+ immunogenicity, using R package txshift (<https://github.com/nhejazi/txshift>.)


References

- Díaz, I. and van der Laan, M. J. (2012). Population intervention causal effects based on stochastic interventions. *Biometrics*, 68(2):541–549.
- Díaz, I. and van der Laan, M. J. (2018). Stochastic treatment regimes. In *Targeted Learning in Data Science: Causal Inference for Complex Longitudinal Studies*, pages 167–180. Springer Science & Business Media.
- Hammer, S. M., Sobieszczyk, M. E., Janes, H., Karuna, S. T., Mulligan, M. J., Grove, D., Koblin, B. A., Buchbinder, S. P., Keefer, M. C., Tomaras, G. D., et al. (2013). Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *New England Journal of Medicine*, 369(22):2083–2092.
- Janes, H. E., Cohen, K. W., Frahm, N., De Rosa, S. C., Sanchez, B., Hural, J., Magaret, C. A., Karuna, S., Bentley, C., Gottardo, R., et al. (2017). Higher t-cell responses induced by DNA/rAd5 HIV-1 preventive vaccine are associated with lower HIV-1 infection risk in an efficacy trial. *The Journal of infectious diseases*, 215(9):1376–1385.
- Rose, S. and van der Laan, M. J. (2011). A targeted maximum likelihood estimator for two-stage designs. *The International Journal of Biostatistics*, 7(1):1–21.

Thank you.

Slides: bit.ly/2019_bstars_shift



 <https://nimahejazi.org>

 <https://github.com/nhejazi>

 <https://twitter.com/nshejazi>