# Supplementary Materials: Using a network-based approach and targeted maximum likelihood estimation to evaluate the effect of adding pre-exposure prophylaxis to an ongoing Test-and-Treat trial

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## 1 Network Generation Process

In order to simulate epidemic spread, we create a collection of networks designed to mimic community structure and mixing patterns found in sexual contact networks. To accomplish this, we employ the Degree-Corrected Stochastic Block model (Karrer and Newman, 2011), which allows for an arbitrary degree distribution and block structure.

### 1.1 Degree Distribution

For each node $i$, its degree is distributed $k_i \sim f$ where $f$ is a the Zipf (powerlaw) distribution with density

$$f(x) = \zeta(\alpha)^{-1} x^{-\alpha}$$

where $\zeta(\alpha)$ is the Zeta function and the $\alpha = 2.5$ is the scale parameter. We note that the value of $\alpha = 2.5$ is commonly observed in empirical networks that have fat-tailed degree distributions.

### 1.2 Block Structure

In addition, this network model allows an arbitrary block structure, or partition of nodes, for which members of each node share a fraction of their edges with each other block. We create networks that are bipartite, show community structure, and allow for members of two blocks to mix more than other block pairs. Let $b_i \in \{1, ..., B\}$ be the block membership for node $i$, with $B = 8$ blocks total. Define the total degree for members of each block $i$ as $\kappa_j := \sum_i k_i \mathbb{I}(b_i = j)$, and the total number of edges $m = \frac{\sum_{j=1}^{B} \kappa_j}{2}$. The Degree-Corrected Stochastic Block Block model specifies the amount of mixing between blocks by specifying mixing matrix $\omega \in \mathbb{N}^{B \times B}$, which details the total number of edges shared between members of pairs of blocks. This matrix requires a constraint to ensure all edges belong to some block pair: $\omega \mathbf{1}^\top \equiv \kappa$, where $\mathbf{1} = \{1, ..., 1\}$ and $\kappa = \{\kappa_1, ..., \kappa_B\}$. In order to create bipartite networks, we further constrain the total number of edges existing between the four blocks of each half of the bipartition to be equal:

$$\sum_{i=1}^{4} \kappa_i = \sum_{j=5}^{8} \kappa_j \tag{1}$$

Before specifying the mixing structure we chose for our paper, we introduce three consistent mixing matrix specifications, each with different properties we detail next. Edges may exist only between the two halves of the network, where each half consists of four blocks each. For notational simplicity, we define the two halves of blocks to be $\mathcal{J}_1 = \{1, 2, 3, 4\}$ and $\mathcal{J}_2 = \{5, 6, 7, 8\}$. $\omega_{\text{community}}$ gives the mixing matrix corresponding to edges only existing in four bipartite communities. It is also possible for only some block pairs to represent a sociodemographic group that mixes less discriminately with other blocks. For example, in the context of HIV, such blocks may stand to represent sex workers. This is accomplished by those blocks sharing edges proportional to the degree of the blocks in the other bipartite half: this is specified by $\omega_{\text{sexworker}}$. Finally, all blocks in each bipartite half may share their edges proportional to the total degree of each other block in the other bipartition half, which is detailed by $\omega_{\text{random}}$. Each of these mixing matrices are detailed below.

$$\omega_{\text{community}} = \begin{bmatrix} 0 & 0 & 0 & 0 & \kappa_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \kappa_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \kappa_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \kappa_4 \\ \kappa_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \kappa_6 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \kappa_7 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \kappa_8 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\omega_{\text{sexworker}} = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\kappa_1\kappa_5}{2m} & \frac{\kappa_1\kappa_6}{2m} & \frac{\kappa_1\kappa_7}{2m} & \frac{\kappa_1\kappa_8}{2m} \\ 0 & 0 & 0 & 0 & \frac{\kappa_1\kappa_6}{2m} & \kappa_2 - \frac{\kappa_1\kappa_6}{2m} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\kappa_1\kappa_7}{2m} & 0 & \kappa_3 - \frac{\kappa_1\kappa_7}{2m} & 0 \\ 0 & 0 & 0 & 0 & \frac{\kappa_1\kappa_8}{2m} & 0 & 0 & \kappa_4 - \frac{\kappa_1\kappa_8}{2m} \\ \frac{\kappa_5\kappa_1}{2m} & \frac{\kappa_5\kappa_1}{2m} & \frac{\kappa_5\kappa_3}{2m} & \frac{\kappa_5\kappa_4}{2m} & 0 & 0 & 0 & 0 \\ \frac{\kappa_5\kappa_2}{2m} & \kappa_6 - \frac{\kappa_5\kappa_2}{2m} & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\kappa_5\kappa_3}{2m} & 0 & \kappa_7 - \frac{\kappa_5\kappa_3}{2m} & 0 & 0 & 0 & 0 & 0 \\ \frac{\kappa_5\kappa_4}{2m} & 0 & 0 & \kappa_8 - \frac{\kappa_5\kappa_4}{2m} & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\omega_{\text{random}} = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\kappa_1\kappa_5}{2m} & \frac{\kappa_1\kappa_6}{2m} & \frac{\kappa_1\kappa_7}{2m} & \frac{\kappa_1\kappa_8}{2m} \\ 0 & 0 & 0 & 0 & \frac{\kappa_2\kappa_5}{2m} & \frac{\kappa_2\kappa_6}{2m} & \frac{\kappa_2\kappa_7}{2m} & \frac{\kappa_2\kappa_8}{2m} \\ 0 & 0 & 0 & 0 & \frac{\kappa_3\kappa_5}{2m} & \frac{\kappa_3\kappa_6}{2m} & \frac{\kappa_3\kappa_7}{2m} & \frac{\kappa_3\kappa_8}{2m} \\ 0 & 0 & 0 & 0 & \frac{\kappa_4\kappa_5}{2m} & \frac{\kappa_4\kappa_6}{2m} & \frac{\kappa_4\kappa_7}{2m} & \frac{\kappa_4\kappa_8}{2m} \\ \frac{\kappa_5\kappa_1}{2m} & \frac{\kappa_5\kappa_2}{2m} & \frac{\kappa_5\kappa_3}{2m} & \frac{\kappa_5\kappa_4}{2m} & 0 & 0 & 0 & 0 \\ \frac{\kappa_6\kappa_1}{2m} & \frac{\kappa_6\kappa_2}{2m} & \frac{\kappa_6\kappa_3}{2m} & \frac{\kappa_6\kappa_4}{2m} & 0 & 0 & 0 & 0 \\ \frac{\kappa_7\kappa_1}{2m} & \frac{\kappa_7\kappa_2}{2m} & \frac{\kappa_7\kappa_3}{2m} & \frac{\kappa_7\kappa_4}{2m} & 0 & 0 & 0 & 0 \\ \frac{\kappa_8\kappa_1}{2m} & \frac{\kappa_8\kappa_2}{2m} & \frac{\kappa_8\kappa_3}{2m} & \frac{\kappa_8\kappa_4}{2m} & 0 & 0 & 0 & 0 \end{bmatrix}$$

Finally, a range of linear combinations of these matrices may be used to specify a mixing matrix with a combination of features described above, provided these combinations sum to 1:

$$\omega = \lambda \cdot \omega_{\text{community}} + \mu \cdot \omega_{\text{sexworker}} + (1 - \lambda - \mu) \cdot \omega_{\text{random}} \tag{2}$$

To create strong community structure, two highly-mixing blocks, and some random mixing between blocks, we selected mixing matrix values $\lambda = 0.1, \mu = 0.8$.

For further details and full Python code to simulate the networks and the epidemic, we refer the reader to Staples (2016).

## 2 Overview of TMLE in a cluster randomized trial

TMLE is a general framework for the construction of double robust, semiparametric, locally efficient, plug-in estimators (van der Laan and Rose, 2011). A TMLE for the sample average treatment effect in a cluster randomized trial can be implemented as follows (Balzer et al., 2016b).

1. Initial estimation of the conditional mean outcome $\mathbb{E}(Y|A^*, W)$, given the treatment assignment of interest $A^*$ and the baseline covariates $W$.

    - This initial regression can be based on a *a priori*-specified "working parametric model" (Rosenblum and van der Laan, 2010) or more data-adaptive methods (Balzer et al., 2016a). We can adjust for cluster-level covariates by simply regressing the cluster-level outcome (cumulative HIV incidence) on the cluster-level treatment assignment and the cluster-level covariates. We can also adjust for individual-level covariates: first regress the individual-level outcome (indicator of seroconversion) on the cluster-level treatment and the individual-level covariates; then aggregate the predicted individual-level outcomes to the cluster-level (Balzer et al., 2016c).

2. Targeting the initial estimator $\hat{\mathbb{E}}(Y|A^*, W)$ with information exposure mechanism $\mathbb{P}(A^* = 1|W) = 0.5$.

    (a) We can treat the exposure mechanism as known. Alternatively, for additional gains in power, we can estimate it with simple or more data-adaptive methods (Balzer et al., 2016a). For example, we can regress the cluster-level treatment assignment on covariates measured at or aggregated to the cluster-level.

    (b) Calculate the "clever covariate" based on the known or estimated exposure mechanism:

$$\hat{H}(A^*, W) = \left( \frac{\mathbb{I}(A^* = 1)}{\hat{\mathbb{P}}(A^* = 1|W)} - \frac{\mathbb{I}(A^* = 0)}{\hat{\mathbb{P}}(A^* = 0|W)} \right).$$

    (c) Run univariate regression of the cluster-level outcome $Y$ on the covariate $\hat{H}(A^*, W)$ with the (logit) of the initial estimator as offset.

    (d) Plug-in the estimated coefficient to yield the targeted update $\hat{\mathbb{E}}^*(Y|A^*, W)$.

3. Parameter estimation with the average difference in the predicted cluster-level outcomes:

$$\text{TMLE} = \frac{1}{n} \sum_{i=1}^{n} \left[ \hat{\mathbb{E}}^*(Y_i|A_i^* = 1, W_i) - \hat{\mathbb{E}}^*(Y_i|A_i^* = 0, W_i) \right]$$

    where $i$ indexes the clusters.

4. Obtain inference with the influence-curve respecting the unit of independence.

For further details and full `R` code, we refer the reader to Balzer (2016). For a more general introduction to Targeted Learning framework, we refer the reader to Petersen and Balzer (2014).

# 3 Supplementary Tables

***Supplementary Table 1.*** *For the targeted maximum likelihood estimator (TMLE), the proportion of times a candidate variable was selected for adjustment during estimation of the outcome regression* $\mathbb{E}(Y|A^*, W)$ *or the treatment mechanism* $\mathbb{P}(A^* = 1|W)$*. For simplicity, we only present the results from Design 2 with the Couples PrEP strategy.*

| | Nothing | Degree | Demo.[a] | N. partners[b] | Village prev. | Assort. | N. components[c] |
|---|---|---|---|---|---|---|---|
| UTT before PrEP on the three-year cumulative HIV incidence | | | | | | | |
| Outcome regression | 0 | 3 | 0 | 82 | 10 | 0 | 4 |
| Exposure mechanism | 84 | 4 | 3 | 1 | 2 | 3 | 3 |
| PrEP in UTT high arm on the four-year cumulative HIV incidence | | | | | | | |
| Outcome regression | 5 | 14 | 5 | 48 | 14 | 5 | 9 |
| Exposure mechanism | 85 | 3 | 3 | 2 | 3 | 2 | 3 |
| PrEP in UTT low* arm on the four-year cumulative HIV incidence | | | | | | | |
| Outcome regression | 4 | 14 | 4 | 49 | 13 | 6 | 10 |
| Exposure mechanism | 85 | 2 | 3 | 2 | 2 | 2 | 3 |
| Main PrEP Effect on the four-year cumulative HIV incidence | | | | | | | |
| Outcome regression | 2 | 8 | 2 | 58 | 18 | 3 | 10 |
| Exposure mechanism | 78 | 5 | 5 | 1 | 3 | 5 | 4 |
| Joint (UTT + PrEP) Effect on the seven-year cumulative HIV incidence | | | | | | | |
| Outcome regression | 0 | 10 | 0 | 68 | 12 | 2 | 8 |
| Exposure mechanism | 87 | 3 | 3 | 1 | 2 | 2 | 2 |

Prev.: prevalence; Assort.: assortativity

Low*: initially lower coverage at 55% and then ramp-up to higher coverage at 85%

[a]Demo.: demographic risk group

[b]N.partners: number of partners infected at baseline

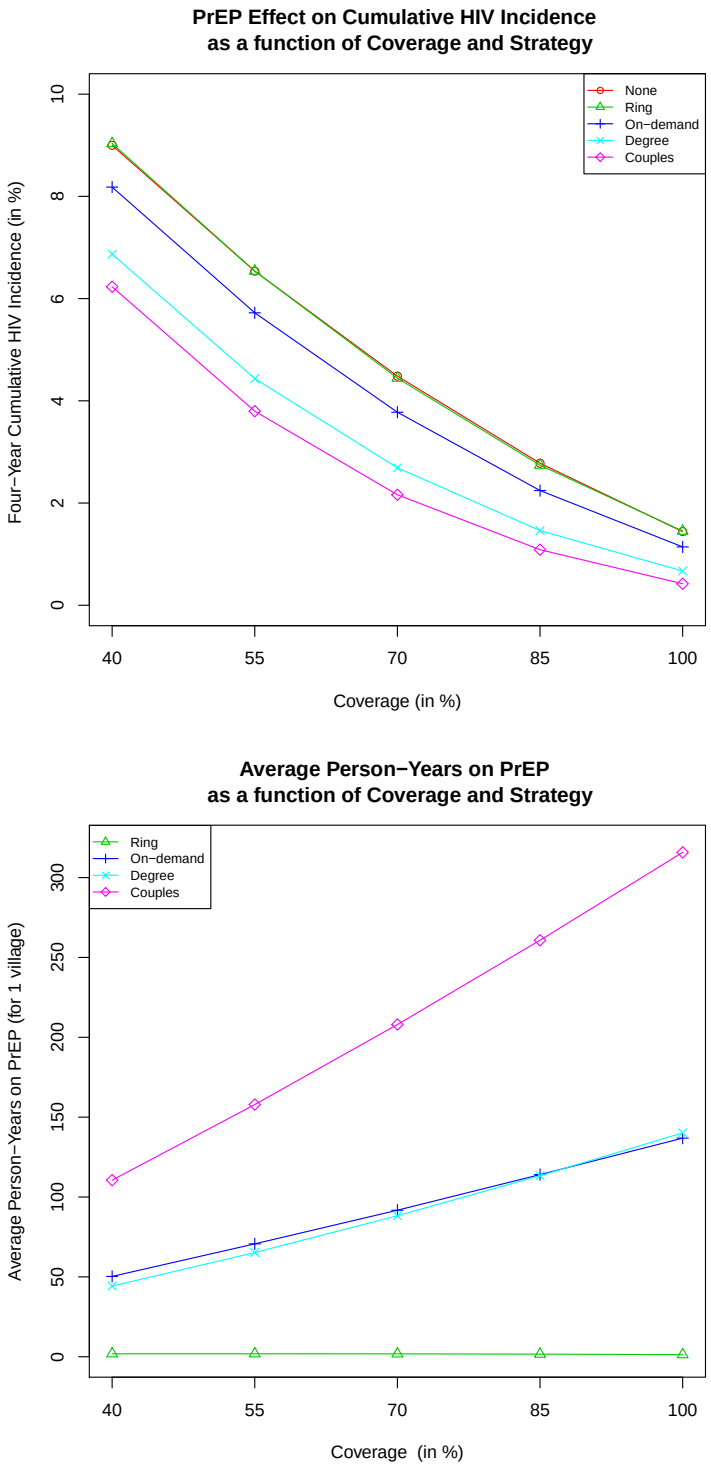
[c]N. components: number of distinct sexual groups

***Supplementary Table 2.*** *Additional effects and estimator performance of the unadjusted estimator and the targeted maximum likelihood estimator (TMLE) over 1000 simulated trials.*

| | True Values | | | Unadjusted | | | TMLE | | |
|---|---|---|---|---|---|---|---|---|---|
| | Int[a] | Con[b] | SATE[c] | MSE[d] | Cov[e] | Power[f] | MSE[d] | Cov[e] | Power[f] |
| UTT without PrEP on the seven-year cumulative HIV incidence | | | | | | | | | |
| Design1: | 7.7 | 15.0 | -7.3 | 4.1E-4 | 98 | 84 | 2.1E-4 | 98 | 97 |
| Design2: | 7.8 | 12.2 | -4.4 | 6.2E-4 | 96 | 37 | 3.4E-4 | 97 | 54 |
| UTT with PrEP on the seven-year cumulative HIV incidence | | | | | | | | | |
| Design2: Ring | 7.8 | 12.2 | -4.5 | 5.8E-4 | 96 | 35 | 6.3E-4 | 96 | 52 |
| Design2: On-demand | 7.3 | 11.7 | -4.5 | 5.4E-4 | 96 | 37 | 4.9E-4 | 98 | 55 |
| Design2: Degree | 6.5 | 10.9 | -4.3 | 4.4E-4 | 96 | 43 | 5.3E-4 | 96 | 59 |
| Design2: Couples | 6.2 | 10.4 | -4.3 | 4.4E-4 | 96 | 37 | 2.6E-4 | 96 | 59 |
| Main UTT Effect on the seven-year cumulative HIV incidence | | | | | | | | | |
| Design2: Ring | 7.8 | 12.2 | -4.5 | 2.7E-4 | 97 | 67 | 1.3E-4 | 98 | 88 |
| Design2: On-demand | 7.5 | 12.0 | -4.5 | 2.9E-4 | 96 | 67 | 1.3E-4 | 98 | 88 |
| Design2: Degree | 7.2 | 11.6 | -4.4 | 2.5E-4 | 97 | 68 | 1.1E-4 | 99 | 88 |
| Design2: Couples | 7.0 | 11.3 | -4.3 | 2.8E-4 | 97 | 66 | 1.3E-4 | 98 | 87 |

[a] Average cumulative HIV incidence under the intervention scenario (%)
[b] Average cumulative HIV incidence under the control scenario (%)
[c] Average value of the SATE (%)
[d] MSE: mean squared error (bias$^2$ + variance) (%)
[e] Coverage: Proportion of times the 95% confidence intervals contained the true value (%)
[f] Attained power: proportion of times the false null hypothesis was rejected (%)

# 4 Supplementary Figures




***Supplementary Figure 1.*** *Top: the four-year cumulative HIV incidence (from study year 3 to year 7) as a function of PrEP strategy and coverage. Bottom: the average person-years on PrEP for 1 village (among eligibles) as a function of PrEP strategy and coverage. Throughout, we define coverage as the proportion of village-members who successfully complete the care cascade (testing, treatment, retention and adherence) for ART or PrEP, as appropriate. Results shown for Design1 only.*

## References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