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Accounting for interactions and complex inter-subject dependency in estimating treatment effect in cluster randomized trials with missing outcomes

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Summary

Semi-parametric methods are often used for the estimation of intervention effects on correlated outcomes in cluster-randomized trials (CRTs). When outcomes are missing at random (MAR), Inverse Probability Weighted (IPW) methods incorporating baseline covariates can be used to deal with informative missingness. Also, augmented generalized estimating equations (AUG) correct for imbalance in baseline covariates but need to be extended for MAR outcomes. However, in the presence of interactions between treatment and baseline covariates, neither method alone produces consistent estimates for the marginal treatment effect if the model for interaction is not correctly specified. We propose an AUG-IPW estimator that weights by the inverse of the probability of being a complete case and allows different outcome models in each intervention arm. This estimator is doubly robust (DR), it gives correct estimates whether the missing data process or the outcome model is correctly specified. We consider the problem of covariate interference which arises when the outcome of an individual may depend on covariates of other individuals. When interfering covariates are not modeled, the DR property prevents bias as long as covariate interference is not present simultaneously for the outcome and the missingness. An R package is developed implementing the proposed method. An extensive simulation study and an application to a CRT of HIV risk reduction-intervention in South Africa illustrate the method.

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Web-Supplementary Materials

Web Appendices, Tables, Figures, simulated data and, R sources implementing the estimators referenced in Sections 3.1, 3.3 and 5.2 are available with this paper at the Biometrics website on Wiley Online Library.

Keywords

Augmentation; Cluster-randomized trials; Generalized estimating equation (GEE); Interactions; Interference; Inverse probability weighting (IPW); Missing at random (MAR); Outcome Model; Propensity Score; R package; Semi-parametric methods

1. Introduction

In clustered randomized clinical trials (CRTs), the unit of treatment assignment is a cluster of subjects, which we also refer to as community. In such settings, outcomes are likely to be correlated among subjects within the same cluster. Often used for estimation, generalized estimating equations (GEE) based on semi-parametric methods (Zeger and Liang, 1986) target marginal effects of treatment. Within clusters, dependence can be modeled using a working correlation structure. Compared to mixed effects models, this approach has the advantage of focusing on population average effects rather than cluster specific effects (which are equal for continuous outcomes) and requires fewer parametric assumptions on the outcome distribution (Hubbard et al., 2010). Moreover, because both the outcome and the missing data mechanism can be modeled, this approach allows doubly robust estimation, which is impossible with mixed effect models. Finally, this approach to estimation is robust to misspecification of the correlation structure. However, challenges arise in developing a consistent and efficient estimator of marginal treatment effects; these include the need to adjust for missing data and accommodate covariate interference (wherein a subject's outcome may be affected by covariates of other subjects) and interactions (wherein the effect of treatment varies by covariate-defined subgroups). We propose a method that addresses these issues and is practical to implement for evaluating novel interventions in CRTs.

In CRTs, covariates may be fully observed even if the outcome is missing. When data are assumed missing completely at random (MCAR) – i.e. the observed process is independent of observed and unobserved information (Rubin, 1976) – the standard GEE approach provides consistent and asymptotically normal (CAN) estimators. If the pattern of missingness depends on observed information but not on missing data, the data are said to be Missing at Random (MAR). In this setting, the standard GEE may yield biased estimates although likelihood-based approaches, such as mixed effect models, can provide unbiased estimators. Imputation (Paik, 1997) or reweighing (Robins et al., 1995) methods can correct for this bias. Although useful if the missingness mechanism is not completely known, multiple imputation requires correct specification of the joint distribution of the outcomes, which is especially difficult when they are correlated and the cluster sizes are large (Beunckens et al., 2008). In this article, we consider the Inverse Probability Weighting (IPW) approach to analyze incomplete data. If the model for the missingness mechanism represents the MAR data generating process, the IPW estimation provides CAN estimators of treatment effects by reweighing complete cases according to the probability of being observed (Liang and Zeger, 1986; Robins et al., 1994).

Recent methodological developments improve estimation efficiency by leveraging baseline covariates; they may be based on targeted maximum likelihood (Moore and van der Laan, 2009) and on augmentation (Robins et al., 1994; Robins, 2000; Tsiatis et al., 2008; Zhang et

al., 2008). Stephens et al. (2012) developed the augmented GEE (AUG) methods in the setting of dependent outcomes such as in CRTs. The AUG adds a term to the standard GEE which relates the outcome to covariates and treatment. Randomization assures that the AUG is CAN even in the case of OM misspecification. However in the case of outcome data that are MAR but not MCAR, the AUG may be biased. There exists theory for extending these methods to MAR data for individual randomized Trials (RTs) with possibly correlated data (Van der Laan and Robins, 2003; Glynn and Quinn, 2010), we focus on the details of implementing the methods in CRTs.

The term interference can refer to different types of relationships among exposures, outcomes and covariates. Interference in RTs arises when one subject's treatment may impact the outcomes of other subjects (Rosenbaum, 2007; Vansteelandt, 2007; Tchetgen Tchetgen and VanderWeele, 2012; Hudgens and Halloran, 2012). A similar phenomenon, confounding by clusters, has been discussed in the context of observational studies (Seaman et al., 2014); we will refer to such confounding as exposure interference. In CRTs all subjects within a cluster receive the same treatment; hence if the clusters are independent as typically assumed in practice, there is no exposure interference measured at the cluster level. Therefore, any choice of working correlation structure for the standard GEE will give a consistent estimator of the marginal treatment effect (Pepe and Anderson, 1994). We will investigate covariate interference among individuals nested within clusters: the setting in which one subject's covariate may impact the outcomes of other subjects.

The IPW and the AUG can be combined in a doubly-robust method we refer to as the DR; we investigate its properties regarding robustness to misspecification of the missing data and outcome generating process. By considering a variety of data generating mechanisms, we investigate settings in which the DR has advantageous properties (consistency and precision) compared to the IPW and the AUG, and discuss the impact of covariate interference and treatment-covariate interactions. This paper is organized as follows. Section 2 introduces notation and assumptions for the IPW and the AUG GEE approaches. Section 3 describes the DR approach, investigates CAN properties and discusses the issue of covariate interference. Section 4 provides a motivating example with data arising from a CRT of an HIV/Sexually Transmitted Infection (STI) risk reduction intervention in South Africa (Jemmott III et al., 2014). Simulation studies regarding bias, relative efficiency and coverage are described in Section 5, and concluding remarks are made in Section 6.

2. Notation, basic models and assumptions

2.1 Notation for CRTs and marginal treatment effect

We consider a study design in which a vector of P baseline covariates $\boldsymbol{X}_{ij}=(X_{ij}^1,\ldots,X_{ij}^P)$ and outcome Y_{ij} are recorded for each subject $j = 1,\ldots, n_i$ in community $i = 1,\ldots, M$. The sample size within each community is assumed fixed by design and non-informative. Our setting compares two arms (treated $A_i = 1$ and control $A_i = 0$); the probability of treatment assignment is known and given by $p = P(A_i = 1)$; extension to a greater number of treatments is straightforward but complicates the notation. In this article, the outcome $\boldsymbol{Y}_i=[Y_{ij}]_{j=1,\ldots,n_i}$ is assumed to be continuous, but extension to other types of outcomes is

straightforward. The vector $\boldsymbol{R}_i=[R_{ij}]_{j=1,\ldots,n_i}$ is the indicator of missingness; Y_{ij} is observed when R_{ij} = 1. The matrix of covariates $\boldsymbol{X}_i=[\boldsymbol{X}_{ij}]_{j=1,\ldots,n_i}$ is assumed to be fully observed and consists only of pre-exposure covariates measured at baseline.

Interest lies in estimating the marginal effect of the treatment given by $M_E^*=E(E(Y_{ij}|A_i=1,\boldsymbol{X}_i)-E(Y_{ij}|A_i=0,\boldsymbol{X}_i))$. For estimating M_E^*, we make inference about the parameters $\boldsymbol{\beta}=(\beta_0,\beta_A)^T$ indexing the marginal model $g(\mu_{ij}(\boldsymbol{\beta},A_i))=g(E(Y_{ij}/A_i))=\beta_0+\beta_A A_i$, where $\boldsymbol{\mu}_i(\boldsymbol{\beta},A_i)=[\mu_{ij}(\boldsymbol{\beta},A_i)]_{j=1,\ldots,n_i}$ and g is a one-to-one link function, which is an identity function in this article. Of particular interest, β_A is equal to M_E^*. Of note, extension to binary outcome Y_{ij} using a logistic function for g and considering odd-ratios is based on the same reasoning.

When the outcome is believed to be MCAR, the missingness process is independent of $\boldsymbol{X}_i$, A_i, and $\boldsymbol{Y}_i$. If one assumes MAR and the missingness pattern is monotone, the probability of missingness can be estimated by a multistep approach by decomposing a monotone missing pattern into multiple uniform missing data models (Robins et al., 1994; Li et al., 2011). In CRTs, any component of $\boldsymbol{Y}_i$ can be missing; hence the missingness pattern is non-monotone. Therefore, we make a stronger assumption than MAR that we refer to as restricted MAR (rMAR): the probability that the outcome for one individual is missing is independent of all outcomes in the cluster, conditional on baseline exposure A_i and cluster characteristics $\boldsymbol{X}_i$. The conditional probability that the outcome is observed is denoted $\boldsymbol{\pi}_{ij}(\boldsymbol{X}_i,A_i)=P(R_{ij}=1/\boldsymbol{X}_i,A_i)$ and is called the propensity score (PS). When data are rMAR, ignoring missing data leads to biased inference if missingness depends both on $\boldsymbol{X}_i$ and A_i. This is because the presence of missing data no longer assures balance of confounding factors between treatment arms. Therefore, analysis must include adjustment for missing data; appropriate models for this adjustment may require treatment-covariate interactions, which may be difficult to specify and require many parameters. Combining the IPW and the AUG, which this paper proposes, makes it possible to obtain consistent estimates of the marginal effect of treatment without explicitly specifying interaction terms while also improving efficiency.

2.2 Inverse Probability Weighted Generalized Estimating Equations (IPW)

In order to account for missing data, semi-parametric estimators based on the IPW are found by solving the estimating equation 1:

$$0=\sum_{i=1}^{M}\underbrace{\boldsymbol{D}_i^T\boldsymbol{V}_i^{-1}\boldsymbol{W}_i(\boldsymbol{X}_i,A_i,\boldsymbol{\eta}_W)\,[\,\boldsymbol{Y}_i-\boldsymbol{\mu}_i(\boldsymbol{\beta},A_i)]}_{\psi_i(\boldsymbol{Y}_i,\boldsymbol{R}_i,A_i,\boldsymbol{\beta},\boldsymbol{\eta}_W)}, \quad (1)$$

where $\boldsymbol{D}_i=\dfrac{\partial\boldsymbol{\mu}_i(\boldsymbol{\beta},A_i)}{\partial\boldsymbol{\beta}^T}$ is the design matrix, $\boldsymbol{V}_i$ is the covariance matrix equal to $\boldsymbol{U}_i^{1/2}\boldsymbol{C}(\boldsymbol{\alpha})\boldsymbol{U}_i^{1/2}$ with $\boldsymbol{U}_i$ a diagonal matrix with elements var(y_{ij}) and $\boldsymbol{C}(\boldsymbol{\alpha})$ is the working correlation structure with non-diagonal terms $\boldsymbol{\alpha}$. For example, for an independence correlation structure $\boldsymbol{\alpha}$ are zero; for exchangeable all the elements of $\boldsymbol{\alpha}$ are identical.

Parameters $\boldsymbol{\alpha}$ could also depend on the treatment group $\boldsymbol{C}(\boldsymbol{\alpha}(A_i))$ but we do not consider this possibility in our implementation. In this article, we estimate the $\boldsymbol{\alpha}$ parameters using moment estimators from the Pearson residuals as in McDaniel et al. (2013). The $n_i \times n_i$ matrix of weights is $\boldsymbol{W}_i(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W) = diag[R_{ij}/\pi_{ij}(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W)]_{j=1,\ldots,n_i}$, where the PS is obtained by fitting a binary response model that regresses the indicator R_{ij} on functions of A_i and $\boldsymbol{X}_{ij}$. The $\boldsymbol{\eta}_W$ are nuisance parameters estimated in the PS. A necessary assumption for this method is that probabilities for the PS are bounded away from zero. Several authors have noted the instability that may arise from small probabilities of observation (i.e. large weights) and proposed use of stabilized or truncated weights; see Seaman and White (2013) for a review. To ensure that the IPW provides a CAN estimator, the PS must include all variables that are associated simultaneously with both the missingness and outcome processes (Brookhart et al., 2006) including treatment-covariate interaction terms (Belitser et al., 2011). In other words, the PS must be correctly specified, in the sense that $\boldsymbol{\pi}_{ij}(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W) = P(R_{ij} = 1 | \boldsymbol{X}_i, A_i)$ for some $\boldsymbol{\eta}_W$.

2.3 Augmented Generalized Estimating Equations (AUG)

For settings with complete data, Stephens et al. (2012) proposed the AUG estimator which can improve efficiency relative to the standard GEE by incorporating baseline covariates. The AUG is constructed by subtracting from the set of GEEs the orthogonal projection of the standard estimating function onto the span of scores corresponding to all smooth parametric models for the treatment assignment mechanism given covariates. The AUG is given in Equation 2:

$$0 = \sum_{i=1}^{M} \left[\underbrace{\boldsymbol{D}_i^T \boldsymbol{V}_i^{-1} (\boldsymbol{Y}_i - \boldsymbol{\mu}_i(\boldsymbol{\beta}, A_i))}_{\tilde{\psi}_i(\boldsymbol{Y}_i, A_i, \boldsymbol{\beta})} + \sum_{a=0,1} p^a (1-p)^{1-a} \boldsymbol{D}_i^T \boldsymbol{V}_i^{-1} \left(\boldsymbol{B}_i(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B) - \boldsymbol{\mu}_i(\boldsymbol{\beta}, A_i = a) \right) \right]. \quad (2)$$

The term $\tilde{\psi}_i(\boldsymbol{Y}_i, A_i, \boldsymbol{\beta})$ is similar to $\psi_i(\boldsymbol{Y}_i, \boldsymbol{R}_i, A_i, \boldsymbol{\beta}, \boldsymbol{\eta}_W)$ in Equation 1 for the IPW except that $\boldsymbol{W}_i$ is set to identity because there is no adjustment for missing data. Definitions for $\boldsymbol{D}_i$ and $\boldsymbol{V}_i$ remain the same. The vector $\boldsymbol{B}_i(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B) = [B_{ij}(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B)]_{j=1,\ldots,n_i}$ is an arbitrary function of $\boldsymbol{X}_i$ given for each treatment arm. The $\boldsymbol{\eta}_B$ are nuisance parameters that must be estimated. The estimator in Equation 2 is most efficient if $\boldsymbol{B}_{ij}(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B)$ is equal to $E(Y_{ij} | \boldsymbol{X}_i, A_i = a)$ (Robins et al., 1994; Zhang et al., 2008). For this reason, we shall refer to $\boldsymbol{B}_i(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B)$ as the outcome model (OM), and describe the OM as correctly specified when $B_{ij}(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B) = E(Y_{ij} | \boldsymbol{X}_i, A_i = a)$ for some $\boldsymbol{\eta}_B$. In the absence of missing data, the AUG remains consistent even if the OM is not correctly specified. Correct specification can lead to substantial efficiency gains compared to the standard GEE. Moreover, in presence of treatment-covariate interactions, it is useful to fit a different regression model for the OM for each treatment group, e.g.

$B_{ij}(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B) = \gamma_0^a + \sum_{r=1}^{P} \gamma_r^a X_{ij}^r$ with $\boldsymbol{\eta}_B = (\gamma_1^0, \ldots, \gamma_P^0, \gamma_1^1, \ldots, \gamma_P^1)$, thereby obviating

the need to fit covariate-treatment interactions terms. In presence of rMAR, the AUG does not ensure consistent estimation; instead, one must combine the AUG with the IPW as we show below.

3. Methods to accommodate missing data, treatment-covariate interactions and covariate interference in CRTs

3.1 Doubly Robust Augmented IPW Generalized Estimating Equations (DR)

We extend the AUG in Equation 2 to account for missing data using the IPW in Equation 1 by subtracting from the set of GEEs the orthogonal projection of $\psi_i(\boldsymbol{Y}_i, \boldsymbol{R}_i, A_i, \boldsymbol{\beta}, \boldsymbol{\eta}_W)$ onto the span of scores corresponding to all smooth parametric models for the missing data process and the treatment assignment mechanism given covariates (Tsiatis, 2006). This gives the following estimating equation (see Web-Supplementary Material B for details):

$$\begin{aligned} 0 = & \sum_{i=1}^{M} \Big[\boldsymbol{D}_i^T \boldsymbol{V}_i^{-1} \boldsymbol{W}_i(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_B)(\boldsymbol{Y}_i - \boldsymbol{B}_i(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W)) \\ & + \sum_{a=0,1} p^a (1-p)^{1-a} \boldsymbol{D}_i^T \boldsymbol{V}_i^{-1} \Big(\boldsymbol{B}_i(\boldsymbol{X}_i, A_i{=}a, \boldsymbol{\eta}_B) - \boldsymbol{\mu}_i(\boldsymbol{\beta}, A_i{=}a) \Big) \Big], \\ = & \sum_{i=1}^{M} \boldsymbol{\Phi}_i(\boldsymbol{Y}_i, \boldsymbol{R}_i, A_i, \boldsymbol{X}_i, \boldsymbol{\beta}, \boldsymbol{\eta}_W, \boldsymbol{\eta}_B). \end{aligned} \tag{3}$$

The $\boldsymbol{D}_i$, $\boldsymbol{V}_i$ and the PS are defined such as in Equation 1, the OM denoted $\boldsymbol{B}_i(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B)$ is defined for each treatment group such as in Equation 2. The estimator denoted $\hat{\beta}_{aug}$ is found by solving the estimating equation given in equation 3. Although analytic solutions sometimes exist, coefficient estimates are generally obtained using an iterative procedure such as the Newton-Raphson method. To get $\hat{\beta}_{aug}$ we use the estimated PS $(\pi_{ij}(\boldsymbol{X}_i, A_i, \hat{\boldsymbol{\eta}}_W))$ and estimated OM $(\boldsymbol{B}_i(\boldsymbol{X}_i, A_i, \hat{\boldsymbol{\eta}}_B))$. As mentioned above, treatment-covariate interactions can be accounted for by fitting OM regressions separately by treatment group. One could also estimate parameters of the PS model separately by treatment groups. This approach, however, may provide less stable results due to variability in the calculation of weights. In this paper, $\hat{\boldsymbol{\eta}}_W$ in $\pi_{ij}(\boldsymbol{X}_i, A_i, \hat{\boldsymbol{\eta}}_W)$ are obtained using a logistic regression and $\hat{\boldsymbol{\eta}}_B$ in $\boldsymbol{B}_i(\boldsymbol{X}_i, A_i, \hat{\boldsymbol{\eta}}_B)$ are obtained using a linear regression. Thus, we treat R_{ij} and $R_{ij'}$ as conditionally independent given A_i and $\boldsymbol{X}_i$. In the presence of correlation of R_{ij} and $R_{ij'}$, one might be able to improve efficiency of estimation of $\boldsymbol{\pi}_{ij}$ and therefore of the marginal treatment effect by accounting for this correlation. Of note, estimation procedures other than generalized linear models could also be used to compute the OM and the PS values. The DR estimator is doubly robust in the sense that it is CAN under correct specification of either the OM (i.e. $B_{ij}(\boldsymbol{X}_i, A_i = a, \boldsymbol{\eta}_B) = E(Y_{ij}|A_i = a, \boldsymbol{X}_i)$ for some $\boldsymbol{\eta}_B$) or the PS (i.e. $\boldsymbol{\pi}_{ij}(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W) = P(R_{ij} = 1|\boldsymbol{X}_i, A_i)$ for some $\boldsymbol{\eta}_W$) (see Web-Supplementary Material Section C1). Implementation in R is available on the CRAN in the package *'CRTgeeDR'*. Source code had been made available as Web-Supplementary material. We note that in contrast with several existing software packages (for example proc GENMOD in SAS (2015)), our

implementation of the weighted GEE, which uses $\boldsymbol{V}_i^{-1}\boldsymbol{W}_i+(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W)$ instead of $\boldsymbol{W}_i^{1/2}(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W)\boldsymbol{V}_i^{-1}\boldsymbol{W}_i^{1/2}(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W)$, guarantees consistency for all choices of working correlation structure (see details in Web-Supplementary Material Section C2 and D).

3.2 Variance of the DR estimator

The variance of $\hat{\beta}_{aug}$ is estimated by the sandwich variance estimator. There are two external sources of variability that need to be accounted for: estimation of $\boldsymbol{\eta}_W$ for the PS and of $\boldsymbol{\eta}_B$ for the OM. We denote $\boldsymbol{\Omega} = (\boldsymbol{\beta}, \boldsymbol{\eta}_W, \boldsymbol{\eta}_B)$ the estimated parameters of interest and nuisance parameters. We can stack estimating functions and score functions for Ω:

$$\boldsymbol{U}_i(\boldsymbol{\Omega})=\begin{pmatrix} \boldsymbol{\Phi}_i(\boldsymbol{Y}_i, \boldsymbol{X}_i, A_i, \boldsymbol{\beta}, \boldsymbol{\eta}_W, \boldsymbol{\eta}_B) \\ \boldsymbol{S}_i^W(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W) \\ \boldsymbol{S}_i^B(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_B) \end{pmatrix},$$

where $\boldsymbol{S}_i^W$ and $\boldsymbol{S}_i^B$ represent the score equations for patients in cluster *i* for the estimation of $\boldsymbol{\eta}_W$ and $\boldsymbol{\eta}_B$ in the PS and the OM. A standard Taylor expansion paired with Slutzky's theorem and the central limit theorem provide the sandwich estimator adjusted for nuisance parameters estimation in the OM and PS. We refer to this as the nuisance-adjusted sandwich estimator:

$$Var(\boldsymbol{\Omega})=E\left[\frac{\partial \boldsymbol{U}_i(\boldsymbol{\Omega})}{\partial \boldsymbol{\Omega}}\right]^{-1^T} \underbrace{E[\boldsymbol{U}_i(\boldsymbol{\Omega})\boldsymbol{U}_i^T(\boldsymbol{\Omega})]}_{\boldsymbol{\Delta}_{adj}} \underbrace{E\left[\frac{\partial \boldsymbol{U}_i(\boldsymbol{\Omega})}{\partial \boldsymbol{\Omega}}\right]^{-1}}_{\boldsymbol{\Gamma}_{adj}^{-1}}. \quad (4)$$

The variance estimator $\widehat{var}(\hat{\beta}_{aug})$ is obtained by estimating unknown quantities upon substituting empirical means for expectations and $\hat{\boldsymbol{\Omega}}=(\hat{\beta}, \widehat{\eta_W}, \widehat{\eta_B})$ for $\boldsymbol{\Omega}$. Thus, the term $\widehat{\Delta_{adj}}$ is given by $\frac{1}{M}\sum_{i=1}^{M}\widehat{\boldsymbol{U}_i}(\hat{\Omega})\widehat{\boldsymbol{U}_i}(\hat{\Omega})^T$ and $\widehat{\boldsymbol{\Gamma}_{adj}}$ is given by $\frac{1}{M}\sum_{i=1}^{M}\frac{\partial \widehat{\boldsymbol{U}_i}(\hat{\boldsymbol{\Omega}})}{\partial \boldsymbol{\Omega}}$

In small sample settings, it is likely that this estimator of the variance of $\hat{\beta}_{aug}$ is biased. We implemented Fay's bias-correction approach, which is particularly suitable for M-estimators (Fay et al. 2001). The term $\widehat{\boldsymbol{\Delta}_{adj}}$ in Equation 4 is replaced by $\widehat{\boldsymbol{\Delta}_{fay}}$ given by $\frac{1}{M}\sum_{i=1}^{M}\left[\widehat{\boldsymbol{H}_i}\widehat{\boldsymbol{U}_i}(\hat{\boldsymbol{\Omega}})\left(\widehat{\boldsymbol{H}_i}\widehat{\boldsymbol{U}_i}(\hat{\boldsymbol{\Omega}})\right)^T\right]$, where $\widehat{\boldsymbol{H}_i}$ is a diagonal matrix with diagonal terms $\widehat{\boldsymbol{H}}_{i[jj]}=\left[1-min\left(q, \left(\frac{\partial \widehat{\boldsymbol{U}_i}(\hat{\boldsymbol{\Omega}})}{\partial \boldsymbol{\Omega}}\widehat{\boldsymbol{\Gamma}_{adj}^i}\right)_{[jj]}\right]\right.$, q = 0.75 is a frequently-used bound.

3.3 Definition of covariate interference and implication for analysis

In previous sections, we discussed covariates measured on the index subject (j), but other subjects' (j') covariates may also impact the outcome for the index subject. An example of a potentially interfering covariate is described by Kaiser et al. (2011) who found a positive association between age of partner and infection with HIV. Similarly, the characteristics of subgroups to which the index case belongs (household, neighborhoods,…), whether known or not, may be interfering covariates (Brumback and He, 2011). In this paper, we consider the phenomenon of covariate interference where there exists at least one individual $j' \neq j$ such that $E(Y_{ij}|\boldsymbol{X}_{ij}) \neq E(Y_{ij}|\boldsymbol{X}_{ij}, \boldsymbol{X}_{ij'})$. That is, even after all covariates for the index subject j have been included in the model, the covariates of individuals other than the index subject still affect the outcome of the index subject j; we refer to such covariates as interfering covariates. See Pepe and Anderson (1994) for a similar definition in longitudinal data and see Seaman et al. (2014); Liu and Hudgens (2014) for an analogous definition in non-randomized clustered data in the context of confounding by cluster and interference. Refer to Web-Supplementary Material Section A for a causal interpretation of covariate-interference.

When interfering covariates affect either the outcome $(E(Y_{ij}|\boldsymbol{X}_{ij}) \neq E(Y_{ij}|\boldsymbol{X}_{ij}, \boldsymbol{X}_{ij'}))$ or the missingness process $(E(R_{ij}|\boldsymbol{X}_{ij}) \neq E(R_{ij}|\boldsymbol{X}_{ij}, \boldsymbol{X}_{ij'}))$, but not both, the DR estimator is CAN even if the interfering covariates are not included in the models, provided that either the PS or the OM is correctly specified. Accounting for covariate interference in the OM increases efficiency if and only if interfering covariates predict the outcome. When such covariates impact both the outcome and the missing data generating processes, they must be included in either the OM or the PS models. Thus, the DR estimator is CAN if the model for either the OM or the PS is correctly specified; i.e. either the PS or the OM includes all the covariates $\boldsymbol{X}_i$ in a model that correctly represents the data generation processes. We acknowledge that this model for interfering covariates is not likely to be known and can be difficult to identify. Different cluster sizes and sub-clustering structures (such as households) may make infeasible the use of regression techniques in the OM or the PS because of the potentially different dimensions of the individual and interfering covariates. Cluster summary measures such as the mean or maximum of individual covariates in the cluster (or sub-groups in each cluster) may nonetheless be useful in incorporating interference covariates in models (Brumback et al., 2010).

4. Application

4.1 Description of the SAM study

We analyze data from the "South African Men" (SAM) study which randomized 22 pair-matched clusters to a health-promotion intervention (control) and an HIV/STI risk-reduction intervention in a CRT design; the study included 1181 South African men who have sex with women. A complete description of the study design can be found in (Jemmott III et al., 2014). We focus on a cross-sectional analysis of these data after one year and ignore matching. The primary outcome of our analysis is the overall percentage of acts of protected intercourse among the total number of acts of intercourse. When the total number of acts of

intercourse is zero, we set the percentage to 100%, as no exposure implies no risk. Secondary outcomes are the percentages of protected acts of intercourse by type of partnership and type of intercourse (vaginal and anal sex with main and casual partners). Descriptive statistics for these outcomes, including proportion of missing observations by type of partner and intercourse are provided in Table 1. Slightly more observations are missing in the HIV/STI intervention group (20.8% versus 17.5%). The overall protection percentage after one year are about 64% for the HIV/STI intervention compared to 60% for the control group.

As the proportion of missing baseline covariates was less than 0.1%, we consider them to be MCAR and exclude observation with missing covariates from the analysis. No community sub-structure, such as household or neighborhood structures, was described in the SAM study. Here we consider potential interfering covariates at a cluster level by taking the mean (or mode for qualitative variables) of baseline measures in the community: $\overline{X_{i\cdot}^k}=\frac{1}{n_i}\sum_{j=1,\ldots,n_i} X_{ij}^k$. For example Hawkes et al. (2013) demonstrated that the mean religiosity score for a community, defined as the mean of individual religiosity score in the community, may have an impact on each individual outcome and missingness in particular regarding sexual behaviors. Table 1 describes socio-demographical individual-level variables and interfering covariates. We provide p-values for Wald tests testing the association of covariates and treatment-covariate interactions with the outcome and the missingness indicator. In this study, there is evidence of interactions of individual covariates with treatment for both the outcome and the missing data generation processes. However, the interfering covariates defined here do not appear to be significantly associated with both the outcome and the missing data generation process.

4.2 Results

We analyze these data with the GEE, the AUG, the IPW and the DR using both independence (−I) and exchangeable (−E) working correlation structures. Variables for the PS, and the OM were selected using a forward stepwise regression (separately for each treatment group) from among all the individual covariates $\boldsymbol{X}_{ij}$ presented in Table 1. We did not include the interfering covariates $(\overline{X_i})$ in the analysis as none impacted both outcome and missingness processes (Table 1). We used the *step* function in R based on the AIC criterion. Results of these selections are given in Web-Supplementary Material F. We describe here the results for the primary outcome. The amount of missingness is larger in the treated arm and increases with age; it decreases with religiosity, good health score, and exercise. The OM patterns are substantially different for treated and control; the only common variable is the CAGE score. In both arms lower alcohol consumption is associated with a greater percentage of protected acts of intercourse. Results are presented in Table 2 for primary and secondary outcomes. With the DR-E, we observe a significant difference of 7.4% (sd=2.9%, p=0.01) in the overall percentage of protected intercourse in the HIV/STI intervention group compared to the control group. Analyses of the secondary outcomes suggest that this result is mainly driven by condom use during vaginal intercourse with a marital partner. The HIV/STI intervention has no significant impact on other outcomes. Using the DR rather than the standard GEE or the AUG has an impact on the treatment effect estimates and associated

standard errors (SE). The difference between these approaches is apparent in the magnitude and direction of the marginal treatment effect estimate. For example, the analysis for the GEE-I (3.8 [−1.0; 8.5]) does not demonstrate a significant effect of the HIV/STI intervention on overall percentage of protected intercourse, whereas this effect is stronger and significant for the DR-I (7.3 [1.6; 13.0]). Both the GEE-I and the AUG-I (5.4 [2.2; 8.7]) are probably biased due to missing data. Using the DR instead of the IPW leads to an increased magnitude of the treatment effect and an increased level of statistical significance: for example, the DR-E (7.4 [1.73; 13.0]) compared to the IPW-E (3.4 [−1.4; 8.3]).

5. Simulation Studies

5.1 Properties of the DR estimator

We consider a setting with continuous outcome Y_{ij} and assignment of treatment A_i at a cluster level with probability $p = 1/2$. We generate a normally distributed covariate X^1_{ij} (independent of A_i) with mean 1 and a standard deviation of 5. For each individual, we define a covariate $\overline{\boldsymbol{X}^1_i}$. which is the mean of $\boldsymbol{X}^1$ for all the subjects in the same cluster: $\overline{\boldsymbol{X}^1_i}=\frac{1}{n_i}\sum_{j=1}^{n_i} X^1_{ij}$. Similarly, we generate $X^2_{ij}\sim\mathcal{N}(2,5)$ and $X^3_{ij}\sim\mathcal{N}(3,5)$; $\overline{\boldsymbol{X}^2_i}$ and $\overline{\boldsymbol{X}^3_i}$ are defined as was $\overline{\boldsymbol{X}^1_i}$ and are possible interfering covariates. The model for simulation is given in Equation 5:

$$\begin{cases} Y_{ij} & =\beta_0^O+\beta_A^O A_i+\beta_1^O X^1_{ij}+\beta_{I1}^O \overline{X^1}_{i.}+\beta_{A1}^O A_i X^1_{ij}+\varepsilon_i^O+\varepsilon_{ij}^O \\ logit(P(R_{ij}=0)) & =\beta_0^M+\beta_A^M A_i+\beta_1^M X^1_{ij}+\beta_{I1}^M \overline{X^1}_{i.}+\beta_{A1}^M A_i X^1_{ij} \end{cases}. \quad (5)$$

The parameters $\boldsymbol{\beta}^O=(\beta_0^O,\beta_A^O,\beta_1^O,\beta_{I1}^O,\beta_{A1}^O)$ are the regressors associated with intercept, treatment, covariate, interfering covariate, treatment-covariate interaction for the outcome model. Parameters $\boldsymbol{\beta}^M$ are the same for the missing data generating process. Scenarios with low correlation among cluster (0.05) were simulated with $\varepsilon_i^O\sim\mathcal{N}(0,0.05)$ and $\varepsilon_{ij}^O\sim\mathcal{N}(0,1.0)$ for cluster and individual random errors; scenarios with high correlation (0.2) were simulated with $\varepsilon_i^O\sim\mathcal{N}(0,0.25)$ and $\varepsilon_{ij}^O\sim\mathcal{N}(0,1.0)$. True correlation structure is exchangeable. We investigate small sample ($M = 10$ and $n_i = (10, 20, 30)$ with probability 1/3 each) and large sample ($M = 100$ and $n_i = (90, 100, 110)$ with probability 1/3 each) properties. In each scenario, we generate 1000 replicates of datasets.

We evaluate the double robustness of the DR estimator in the setting of large and small sample with low correlation, but similar results are observed for large correlation. We investigate models of analysis with OM and PS correctly specified (TRUE), misspecified (MISS) and partially specified omitting treatment-covariate interactions (NONE). Table 3 describes the data generation process, provides the formulations of the models of analysis, and shows the results from analysis; on average, 26% of outcomes were missing and the average ICC was 0.08. When there is no missing data, the traditional GEE is consistent because of randomization. When outcome data are MAR but not MCAR, the GEE and the

AUG analysis are biased (−1.7 for the GEE-I and −1.8 for the AUG-I). When either the OM or the PS models or both are correctly specified there is negligible estimated bias for the DR – a finding that confirm consistency. In small samples, this bias is bigger when only the PS is correct because the weights are estimated with lower accuracy. Using the more common choice of implementation for the weighted GEE $\boldsymbol{W}_i^{1/2}(\boldsymbol{\eta}_W)\boldsymbol{V}_i^{-1}\boldsymbol{W}_i^{1/2}(\boldsymbol{\eta}_W)$ leads to very high bias if an exchangeable correlation structure is used (0.374 if the OM is correct and 858 if it is not, for large sample). When the OM is correct the coverage remains around 95% (see Table 2 in Web-Supplementary Material E). Using $\boldsymbol{V}_i^{-1}\boldsymbol{W}_i(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W)$ in the implementation of weights addresses this problem and permits the use of correlation structures other than independence. The IPW with correct PS also corrects the bias (−0.01) but is less efficient than the DR approach; coverage is close to the nominal value of 95%. In small samples, the empirical SE are underestimated. By contrast, in the large sample setting, using the nuisance-adjusted sandwich estimator for the DR leads to good estimates of the asymptotic SE (0.0263) compared to the empirical SE (0.0266) over 1000 replicates. Moreover, we observe that the coverage using the DR is comparable to that of the GEE with complete data. Finally, we note that when the treatment-covariate interactions are ignored in the PS and only accounted for in the OM by fitting a different regression in each treatment group, the DR approach is also consistent and achieve same precision as when both the PS and the OM are correct (0.0014 and SE=0.027 for OM.TRUE.PS.NONE and 0.0013 SE=0.029 for OM.TRUE.PS.TRUE).

Table 4 presents the results of analyses with the GEE, the IPW, the AUG and the DR that investigate the impact of correlation of the outcome in the data with small and large sample. The average percentage of missing outcomes is 23%; the average ICC is 0.04 for low correlation and 0.21 for high correlation. We analyzed the data using a PS and an OM model that was fit using a stepwise variable selection from among all of the individual and interfering covariates described above. The GEE and the AUG estimates are systematically biased because there is no correction for missing data. The IPW is also biased because the PS is incorrect in that it omits treatment-covariate interactions. The DR estimates are consistent in all analyses. In small sample settings, the empirical SE is underestimated even when using nuisance-adjusted SE, but estimation is improved by Fay's correction. Nonetheless, the coverage remained lower than 86%, but it improves for large samples. Finally, when there is low correlation in the outcome, the robust SE better approximate the empirical SE.

5.2 Simulations mimicking the SAM Study

To consider more complex settings, we mimic the SAM study (see Section 4). We simulate the following individual-level covariates: employment $(\mathrm{EMP}\sim\mathscr{B}(0.25))$, marital status $(\mathrm{MARI}\sim\mathscr{B}(0.23))$, age $(\mathrm{AGE}\sim\mathscr{N}(27;7))$, religiosity $(\mathrm{REL}\sim\mathscr{N}(0,0.8))$, the CAGE score (from a multinomial of probabilities $\mathrm{CAGE}\sim\mathscr{M}(0.3;0.1;0.1;0.2;0.3)$ for modalities 0,1,2,3 and 4), the HIV score $(\mathrm{HIV}\sim\mathscr{N}(14;4))$ and the condom knowledge score $(\mathrm{CDM}\sim\mathscr{N}(3;1))$. Interfering covariates are generated as means for quantitative variables or modes for qualitative variables of the individual-level variables in each of the community (as was done for $\overline{\boldsymbol{X}^1}$, $\overline{\boldsymbol{X}^2}$ and $\overline{\boldsymbol{X}^3}$ in Section 5.1). We generate data from the model in Equation 6. In

simulating the outcome, we add cluster random errors to create an exchangeable correlation structure with $\varepsilon_i^O \sim \mathcal{N}(0,5)$ and an individual random effects $\varepsilon_{ij}^O \sim \mathcal{N}(0,4)$. This provides an outcome correlation among clusters of 0.07. We analyzed the data using a PS and an OM composed of all the covariates described above with a stepwise variable selection. Table 5 shows the bias, SE, and coverage of the methods we consider based on 1000 replicates for the estimation of the parameter M_E^*=5.73. The percentage of missing outcomes is 21% and the average empirical ICC is 0.06.

$$\begin{cases} Y_{ij} = 60+40A_i - 9.0\mathrm{EMP}_{ij} - 8.0\mathrm{MARI}_{ij}+1.0\mathrm{CDM}_{ij}+5.0\mathrm{REL}_{ij} \\ \quad +\underbrace{A_i[-2.0\mathrm{AGE}_{ij}+8.5\mathrm{EMP}_{ij}+3.5\mathrm{MARI}_{ij}+1.5\mathrm{HIV}_{ij} - 2.0\mathrm{CAGE}_{ij}+2.0\mathrm{REL}_{ij}]}_{\text{Interactions}} \\ \quad \underbrace{-0.5\overline{\mathrm{AGE}_{i.}} - 7.0\overline{\mathrm{CDM}_{i.}} - 5\overline{\mathrm{REL}_{i.}}+1.0\overline{\mathrm{HIV}_{i.}}}_{\text{covariate interference}}+\varepsilon_i^O+\varepsilon_{ij}^O \\ logit[P(R_{ij}=0)] = -3.0+2.0A_i+0.01\mathrm{AGE}_{ij} - 0.1\mathrm{HIV}_{ij}+\underbrace{A_i[-0.1\mathrm{AGE}_{ij} - 0.2\mathrm{HIV}_{ij}]}_{\text{Interactions}} \\ \quad \underbrace{+0.02\overline{\mathrm{AGE}_{i.}}+0.2\overline{\mathrm{CDM}_{i.}}+0.2\overline{\mathrm{CAGE}_{i.}}}_{\text{covariate interference}} \end{cases} \quad (6)$$

Table 5 provides the estimates the marginal treatment effect for small sample and for the same sample size as that of the SAM data. The GEE, the AUG and the IPW yield biased results whereas the DR has small bias justifying its use to analyse the data even ignoring covariate interference. Fay's correction with coverage around 92% in small sample and 95% in large sample achieve good accuracy. Figure 2 in Web-Supplementary Material C3 represents the histograms of estimates over the 1000 replicates together with the true value of marginal treatment effect. It displays the bias of the GEE, the AUG and the IPW estimators compared to the DR and supports the approximate normal distribution of the DR estimator.

6. Discussion

We propose a doubly robust method for the estimation of the marginal effect of treatment in CRTs with continuous data subject to rMAR – an assumption that arises because missingness is non-monotone in CRTs. Extension to binary or other outcomes is straightforward, provided that there is a one-to-one link function h such that: $\mu_{ij} = h(\boldsymbol{X}_i, A_i)$. We extend the IPW approach proposed by Robins et al. (1995) and the AUG approach for CRTs proposed by Stephens et al. (2012). To be CAN, the DR estimator requires that either the OM or PS model be correctly specified regardless of the choice of the working correlation matrix. Interfering covariates can be ignored if either the OM or the PS is correctly specified. In presence of treatment-covariate interactions, if the PS is not correctly specified, covariates that interact with treatment on the outcome must be included in the OM. We accommodate these treatment-covariate interactions by modeling the OM separately for each treatment group. Covariates for the OM and the PS may be selected

using automatic variable selection procedures such as a stepwise procedure, and may be at the cluster level or individual level.

We recommend using $\boldsymbol{V}_i^{-1}\boldsymbol{W}_i(\boldsymbol{X}_i, A_i, \boldsymbol{\eta}_W)$ to ensure consistency of the IPW and the DR for CRTs, rather than the conventional implementation, $\boldsymbol{W}_i^{1/2}(\boldsymbol{\eta}_W)\boldsymbol{V}_i^{-1}\boldsymbol{W}_i^{1/2}(\boldsymbol{\eta}_W)$, available in several software packages of the weighted GEE. See Tchetgen Tchetgen et al. (2012) for a similar result for longitudinal data with observation-specific weights. If a working independence correlation structure is used, then the two implementations lead to the same result. When $\boldsymbol{W}_i^{1/2}(\boldsymbol{\eta}_W)\boldsymbol{V}_i^{-1}\boldsymbol{W}_i^{1/2}(\boldsymbol{\eta}_W)$ and an arbitrary correlation structure is used in the DR, estimation of marginal treatment effect is consistent only if the OM is correctly specified. We provide an R package called *CRTgeeDR* that implements the proposed DR estimator. The application of our methods to data from the SAM study showed an effect of HIV/STI intervention on the percentage of protected intercourse (Jemmott III et al., 2014) that reached a 0.05 level of significance. Moreover, results of the analysis that distinguishes among different types of partners and of sexual behavior may be useful in targeting future interventions. Our approach allows a situation that we denoted covariate interference in CRTs, and thus extends ideas of adjustment of time-varying covariates in longitudinal responses (Pepe and Anderson, 1994; Tchetgen Tchetgen et al., 2012). Since treatment is randomized at a cluster level and we consider a marginal mean model which only includes treatment, the covariate interference have a different implication for analysis than exposure interference in causal framework (Liu and Hudgens, 2014) or confounding by cluster in observational studies (Berlin et al., 1999; Huang and Leroux, 2011). However, when there are interactions between X_{ij}^r and A_i exposure and covariate interference are related; in this case, individual ij may be seen as receiving pseudo-treatment $A_i X_{ij}^r$. For such a setting, our work may be seen as extending the notion of exposure interference in RTs to CRTs and is related to the work of Ogburn and VanderWeele (2014). In any case, modeling covariate interference may lead to substantial gains of efficiency if they predict the outcome. Therefore, it may be profitable to develop methods that make use of contact network information to inform the selection of interfering covariates. Finally the impact of violation of the rMAR assumption required for the consistency of the DR estimates that resulted from a MNAR missingness mechanism can be investigated by performing sensitivity analysis (Rotnitzky et al., 1998; Vansteelandt et al., 2007).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive statistics of outcomes, sociodemographic individual covariates and interfering covariates by intervention group in SAM study.

Descriptive Statistics of the outcomes				
	HIV/STI		**Control group**	
	Mean [IQR]	**% missing**	**Mean [IQR]**	**% missing**
Primary outcome for percentage of protection *(Y)*				
Overall	64% [26; 100]	20.8%	60% [22; 100]	17.5%
Secondary outcomes for percentage of protection (Y^1, Y^2,Y^3 and Y^4)				
Main partner vaginal sex	61% [22; 100]	10.2%	56% [0; 100]	9.3%
Casual partners vaginal sex	68% [33; 100]	19.7%	68% [33; 100]	17.1%
Main partner anal sex	37% [0; 68]	11.2%	52% [0; 100]	8.6%
Casual partners anal sex	35% [0; 100]	15.1%	31% [0; 100]	12.8%

Descriptive Statistics of the covariates						
			p-value for association with			
	HIV/STI	**Control group**	**Y***		**P(Y observed)****	
	Mean [IQR]	**Mean [IQR]**	$\eta_2^O \neq 0$	$\eta_3^O \neq 0$	$\eta_2^M \neq 0$	$\eta_3^M \neq 0$
Individual covariates X_{ij}						
Age	26 [21; 30]	26.5 [21; 31]	0.41	0.13	**0.03**	0.18
Employment Yes	23%	26%	**0.04**	0.17	**0.01**	**<0.001**
Married Yes	23%	24%	**0.05**	0.76	0.68	0.50
Education Yes	46%	42%	0.58	**<0.001**	0.76	**0.05**
Number of children	1.5 [0; 2]	1.7 [0;2]	0.21	0.12	0.25	0.31
Wealth	5.3 [4; 7]	5.3 [4; 7]	0.77	0.96	0.25	0.54
Social desirability	3.4 [3.2; 3.4]	3.4 [3.2; 3.4]	0.87	0.33	**0.04**	0.34
Religiosity	0.01 [−0.7;0.7]	0.00[−0.7;0.6]	0.46	0.25	**0.07**	0.69
HIV/STI Knowledge	14.3 [12; 17]	14.1 [12; 17]	0.13	0.93	0.37	**0.03**
Condom Behaviors	3.7 [3.3;4]	3.7 [3.3;4.1]	**<0.001**	0.36	0.16	0.33
Condom Knowledge	3.1 [3; 4]	3.1 [3; 4]	0.41	0.57	0.21	**0.06**
Condom Efficacy	3.9 [3.7;4.2]	3.9 [3.7;4.2]	**0.01**	0.31	0.97	0.42
Condom Peer norm	3.7 [3.4;4.1]	3.7 [3.4;4]	**<0.001**	0.71	0.49	0.32
Never had HIV test	20%	21%	0.61	0.80	0.74	0.34
Sexual Activity Yes	84%	84%	0.71	**0.06**	0.53	0.77
Eating attitude	4.2 [4;5]	4.2 [3.7;5]	0.76	**0.01**	0.74	0.53
Exercise Yes	43%	42%	0.99	**0.04**	0.12	0.46
CAGE > = 2	62%	58%	0.22	0.41	0.18	**0.08**
Health Knowledge	10.8 [9; 12]	10.6 [9; 13]	0.51	0.38	0.59	0.83

Descriptive Statistics of the covariates						
	HIV/STI	Control group	p-value for association with Y*		p-value for association with P(Y observed)**	
	Mean [IQR]	Mean [IQR]	$\eta_2^O \neq 0$	$\eta_3^O \neq 0$	$\eta_2^M \neq 0$	$\eta_3^M \neq 0$
Interfering covariates $\overline{X_{i\cdot}} = \frac{1}{n_i}\sum_{j=1,\ldots,n_i} X_{ij}$						
Mean Age	26 [25;27]	27 [26;28]	0.39	0.96	**0.05**	**0.10**
Mean Education Yes	27%	8%	0.58	0.61	0.72	1.00
Mean Number of children	1.6 [1.2; 2.1]	1.7 [1.1;2.1]	0.81	0.67	0.14	0.59
Mean Wealth	5.4 [4.4;6.2]	5.2 [4.4;6.1]	0.45	0.38	0.23	0.92
Mean Social desirability	3.4 [3.3;3.4]	3.4 [3.3;3.4]	0.16	0.44	0.60	0.85
Mean Religiosity	0.00 [−0.1;0.1]	0.00 [−0.1;0.1]	0.84	0.70	0.18	0.94
Mean HIV/STD Knowledge	14.2 [14; 15]	13.9 [13;14]	0.37	0.23	**0.01**	0.45
Mean Condom Behaviors	3.7 [3.6;3.8]	3.7 [3.7;3.8]	0.37	0.40	**0.02**	0.95
Mean Condom Knowledge	3.1 [2.9;3.3]	3.1 [2.9;3.2]	0.52	0.21	0.15	0.32
Mean Condom Efficacy	3.9 [3.7;4.0]	3.9 [3.8;4.0]	0.23	0.38	0.21	0.58
Mean Condom peer norm	3.7 [3.6;3.8]	3.7 [3.6;3.7]	0.23	0.52	**<0.001**	0.01
Mean Eating attitude	4.2 [4.1;4.3]	4.2 [4.0;4.3]	0.71	0.15	0.25	**0.07**
Mean Exercise Yes	76%	82%	0.43	0.53	**0.10**	0.82
Mean CAGE > =2	63%	37%	0.99	0.79	0.71	0.41
Mean Health Knowledge	10.7 [10.5;11]	10.6 [10.3;10.8]	**0.10**	**0.10**	0.15	0.73

* Wald test for η_2^O and η_3^O in the regression $Y = \eta_0^O + \eta_1^O A + \eta_2^O X + \eta_3^O AX$

** Wald test for η_2^M and η_3^M in the regression $logit[P(R=1)] = \eta_0^M + \eta_1^M A + \eta_2^M X + \eta_3^M AX$

Table 2

Analysis of effect of STI/HIV intervention on overall percentage of protected intercourses during the last 3 months one year after intervention (primary outcome) and stratified by intercourse types (secondary outcomes) in SAM study with the GEE, the IPW, the AUG and the DR.

	Independence (−I)			Exchangeable (−E)		
	$\hat{\beta}_A$	SE	p-value	$\hat{\beta}_A$	SE	p-value
Overall percentage of protected intercourse (Y)						
GEE	3.751	2.419	0.121	3.738	2.361	0.113
IPW	3.445	2.558	0.178	3.429	2.488	0.168
AUG	5.414	1.665	0.001	5.478	1.633	0.001
DR	7.341	2.923	0.012	7.386	2.885	0.010
Percentage of protected vaginal intercourse with marital partner (Y^1)						
GEE	5.805	2.689	0.031	5.761	2.67	0.031
IPW	5.660	2.720	0.037	5.626	2.698	0.037
AUG	6.550	1.811	<0.001	6.518	1.794	<0.001
DR	7.254	2.542	0.004	7.273	2.50	0.004
Percentage of protected vaginal intercourse with casual partner (Y^2)						
GEE	−0.621	4.180	0.882	−0.497	4.164	0.905
IPW	−1.500	4.182	0.720	−1.356	4.17	0.745
AUG	−1.191	2.638	0.652	−1.121	2.624	0.669
DR	−2.103	4.077	0.606	−2.018	4.058	0.619
Percentage of protected anal intercourse with marital partner (Y^3)						
GEE	−0.983	1.083	0.364	−0.972	1.081	0.369
IPW	−0.934	1.087	0.390	−0.921	1.085	0.396
AUG	−0.951	0.684	0.164	−0.954	0.684	0.163
DR	−0.835	1.005	0.406	−0.819	1.003	0.414
Percentage of protected anal intercourse with casual partner (Y^4)						
GEE	0.013	1.201	0.991	−0.002	1.204	0.998
IPW	−0.003	1.181	0.998	−0.019	1.184	0.987

	Independence (–I)			Exchangeable (–E)		
	$\hat{\beta}_A$	SE	p-value	$\hat{\beta}_A$	SE	p-value
AUG	−0.467	0.834	0.576	−0.476	0.837	0.570
DR	−0.963	1.207	0.425	−0.971	1.208	0.421

Table 3

Properties for the Doubly robust estimator (DR) compared to the GEE, the IPW and the AUG using the data generation mechanism from Equation 5 with covariate interference for the outcome and missing data generation process. Misspecified (.MISS), correctly specified (.TRUE) and partially specified without treatment-covariate interactions (.NONE) OM and PS are investigated. Statistics for 1000 replicates are the bias compared to $M_E^*=2.0$, the empirical standard errors over the replicates, the mean asymptotic nuisance-adjusted standard error and the coverage with independence (−I) and exchangeable (−E) working correlation matrix.

				Standard Error (SE)				Coverage	
		Bias		Empirical		Robust		95 %	
	M_E^*	−I	−E	−I	−E	−I	−E	−I	−E
Small sample *M = 10,* n_i = (10, 20, 30) with probability 1/3 each, **Low correlation**									
GEE (no missing)	2.0	0.0186	0.0171	0.6553	0.6598	0.5629	0.5682	93.0	92.9
GEE	2.0	−1.7186	−1.7166	0.5717	0.5724	0.5074	0.4306	12.8	7.2
IPW.PS.TRUE	2.0	−0.1623	−0.1689	1.1447	1.1473	0.7987	0.8161	83.9	84.7
AUG.OM.TRUE	2.0	−1.8142	−1.8134	0.4530	0.4148	0.8751	0.8699	39.4	38.0
DR.OM.MISS.PS.TRUE	2.0	−0.0127	−0.0366	2.7327	2.6793	1.4029	1.3985	92.0	92.0
DR.OM.TRUE.PS.MISS	2.0	0.0011	0.0001	0.1544	0.1545	0.1287	0.1330	86.0	87.5
DR.OM.TRUE.PS.TRUE	2.0	−0.0017	−0.0022	0.1881	0.1838	0.1413	0.1447	86.9	87.4
DR.OM.TRUE.PS.NONE	2.0	0.0006	−0.0003	0.1612	0.1608	0.1330	0.1368	85.8	87.8
Large sample *M* = 100, n_i = (90, 100, 110) with probability 1/3 each, **Low correlation**									
GEE (no missing)	2.0	0.0042	0.0043	0.1156	0.1157	0.1155	0.1156	94.3	94.5
GEE	2.0	−1.7335	−1.7321	0.1015	0.1013	0.0994	0.0994	0.0	0.0
IPW.TRUE	2.0	−0.0113	−0.0108	0.2626	0.2621	0.2507	0.2510	93.5	93.9
AUG.TRUE	2.0	−1.8021	−1.8024	0.0694	0.0664	0.2556	0.2550	0.0	0.0
OM.MISS.PS.TRUE	2.0	−0.0089	−0.0079	0.3127	0.3105	0.3937	0.3940	99.3	99.1
OM.TRUE.PS.MISS	2.0	0.0013	0.0014	0.0259	0.0259	0.0256	0.0257	95.2	95.7
OM.TRUE.PS.TRUE	2.0	0.0013	0.0014	0.0284	0.0284	0.0285	0.0285	95.8	96.0
OM.TRUE.PS.NONE	2.0	0.0014	0.0014	0.0266	0.0266	0.0263	0.0263	95.2	95.1

Marginal model for the GEE:

$$\mu_{ij}(\boldsymbol{\beta}, A_i) = \beta_0 + \beta_A A_i$$

OM is fitted for each treatment group $A_i = a$:

$$\begin{array}{ll} \text{OM. TRUE} & B_{ij}(\boldsymbol{X}_i, A_i{=}a) = \gamma_0^a + \gamma_1^a X_{ij}^1 + \gamma_2^a \overline{X^1}_{i.} \\ \text{OM. MISS} & B_{ij}(\boldsymbol{X}_i, A_i{=}a) = \gamma_0^a + \gamma_1^a X_{ij}^2 \end{array}$$

PS is fitted for the whole dataset:

$$\begin{array}{ll} \text{PS. TRUE} & \pi_{ij}(\boldsymbol{X}_i, A_i) = expit\left(\gamma_0^M + \gamma_A^M A_i + \gamma_1^M X_{ij}^1 + \gamma_2^M \overline{X^1}_{i.} + \gamma_3^M A_i X_{ij}^1\right) \\ \text{PS. MISS} & \pi_{ij}(\boldsymbol{X}_i, A_i) = expit\left(\gamma_0^M + \gamma_A^M A_i + \gamma_1^M X_{ij}^2\right) \\ \text{PS. NONE} & \pi_{ij}(\boldsymbol{X}_i, A_i) = expit\left(\gamma_0^M + \gamma_A^M A_i + \gamma_1^M X_{ij}^1 + \gamma_2^M \overline{X^1}_{i.}\right) \end{array}$$

Table 4

Sample size effect and correlation magnitude effects for data generation mechanism given in Equation 5 with $\boldsymbol{\beta}^O = (1,1,1,1,1)$ and $\boldsymbol{\beta}^M = (-3, 1/2, 1/2, 1/2, 1/2)$. Statistics for 1000 replicates are the bias compared to M_E^*, the empirical standard errors over the replicates, the mean asymptotic nuisance-adjusted standard errors and the coverage for the GEE, the IPW, the AUG and the DR with independence (−I) and exchangeable (−E) working correlation matrix.

				Standard Error (SE)						Coverage			
		Bias		Empirical		Robust		Fay's		Robust		Fay's	
	M_E^*	−I	−E	−I	−E	−I	−E	−I	−E	−I	−E	−I	−E
Small sample $M = 10$, $n_i = (10, 20, 30)$ with probability 1/3 each, **Low correlation**													
GEE	2.0	−1.7473	−1.7479	0.4351	0.4360	0.3963	0.3256	0.4559	0.4603	0.8	2.3	3.9	4.9
IPW	2.0	−1.0130	−1.0130	0.6793	0.6842	0.5538	0.5591	0.6735	0.6766	49.0	49.2	59.8	59.9
AUG	2.0	−1.8099	−1.8111	0.3371	0.3269	0.8362	0.8353	0.8834	0.8817	29.7	29.1	40.1	39.2
DR	2.0	0.0008	0.0006	0.1552	0.1586	0.1127	0.1140	0.1190	0.1201	84.8	83.8	86.0	86.2
Large sample $M = 100$, $n_i = (90,100,110)$ with probability 1/3 each, **Low correlation**													
GEE	2.0	−1.7335	−1.7321	0.1015	0.1013	0.0985	0.0727	0.0994	0.0994	0.0	0.0	0.0	0.0
IPW	2.0	−0.9955	−0.9952	0.1514	0.1517	0.1559	0.1563	0.1588	0.1592	0.2	0.2	0.2	0.2
AUG	2.0	−1.8019	−1.8022	0.0695	0.0664	0.2556	0.2550	0.2569	0.2563	0.0	0.0	0.0	0.0
DR	2.0	0.0016	0.0017	0.0265	0.0265	0.0262	0.0263	0.0264	0.0264	95.1	95.0	95.1	95.2
Small sample $M = 10$, $n_i = (10, 20, 30)$ with probability 1/3 each, **High correlation**													
GEE	2.0	−0.0086	−0.0086	0.5265	0.5314	0.4701	0.4721	0.5651	0.5657	88.5	88.4	92.9	92.7
IPW	2.0	−1.0221	−1.0229	0.7026	0.7083	0.5776	0.5829	0.7015	0.7044	52.4	52.2	62.2	61.5
AUG	2.0	−1.7985	−1.7987	0.5058	0.5084	0.8748	0.8727	0.9243	0.9209	35.8	35.8	45.1	45.5
DR	2.0	0.0098	0.0062	0.4328	0.4407	0.2469	0.2480	0.2607	0.2614	77.4	77.7	79.7	79.6
Large sample $M = 100$, $n_i = (90, 100, 110)$ with probability 1/3 each, **High correlation**													
GEE	2.0	−1.7325	−1.7312	0.1145	0.1141	0.1121	0.0753	0.1132	0.1132	0.0	0.0	0.0	0.0
IPW	2.0	−0.9945	−0.9940	0.1618	0.1620	0.1652	0.1656	0.1682	0.1686	0.2	0.2	0.2	0.2
AUG	2.0	−1.8014	−1.8017	0.0787	0.0761	0.2587	0.2581	0.2600	0.2594	0.0	0.0	0.0	0.0
DR	2.0	0.0029	0.0032	0.0609	0.0610	0.0590	0.0590	0.0593	0.0593	94.7	94.6	94.7	94.6

Marginal model for the GEE:

$$\mu_{ij}(\boldsymbol{\beta}, A_i) = \beta_0 + \beta_A A_i$$

OM in AUG and DR is fitted for each treatment group $A_i = a$ using a stepwise regression:

$$B_{ij}(\boldsymbol{X}_i, A_i = a) = \text{stepwise}(X^1_{ij}, X^2_{ij}, X^3_{ij}, \overline{X^1}_{i.}, \overline{X^2}_{i.}, \overline{X^3}_{i.})$$

PS in DR and IPW is fitted for the whole dataset using a stepwise regression:

$$logit(\pi_{ij}(\boldsymbol{X}_i, A_i)) = \text{stepwise}(\boldsymbol{A}_i, X^1_{ij}, X^2_{ij}, X^3_{ij}, \overline{X^1}_{i.}, \overline{X^2}_{i.}, \overline{X^3}_{i.})$$

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Table 5

Simulation of the scenario described in Equation 6 mimicking the SAM study data. Statistics for 1000 replicates are the bias compared to M_E^*, the empirical standard errors over replicates, the mean asymptotic nuisance-adjusted standard error, and the coverage for the GEE, the IPW, the AUG and the DR with independence (−I) and exchangeable (−E) working correlation matrix.

				Standard Error (SE)						Coverage			
		Bias		Empirical		Robust		Fay's		Robust		Fay's	
	M_E^*	−I	−E	−I	−E	−I	−E	−I	−E	−I	−E	−I	−E
Small sample $M = 10$, $n_i = (10, 20, 30)$with probability 1/3 each													
GEE	5.73	2.214	2.213	1.330	1.329	1.829	1.848	1.359	1.363	89.4	88.7	59.4	59.7
IPW	5.73	0.536	0.537	1.333	1.333	1.214	1.214	1.470	1.471	86.5	86.4	92.1	92.1
AUG	5.73	0.173	0.173	0.973	0.973	0.878	0.878	0.925	0.925	88.6	88.6	89.9	89.9
DR	5.73	−0.104	−0.104	1.102	1.101	0.932	0.931	0.982	0.982	90.3	90.3	92.0	92.0
SAM-like sample $M = 50$, $n_i = (20, 30, 30)$ with probability 1/3 each													
GEE	5.73	2.347	2.343	0.308	0.308	0.532	0.466	0.308	0.309	0.0	0.0	0.0	0.0
IPW	5.73	0.622	0.623	0.303	0.303	0.317	0.317	0.323	0.323	50.7	50.7	52.1	52.1
AUG	5.73	0.215	0.215	0.222	0.222	0.230	0.230	0.232	0.232	85.1	85.1	85.2	85.2
DR	5.73	0.037	0.026	0.259	0.260	0.252	0.253	0.254	0.255	94.6	95.3	94.6	95.4

Marginal model for the GEE:

$$\mu_{ij}(\boldsymbol{\beta}, A_i) = \beta_0 + \beta_A A_i$$

OM in AUG and DR is fitted for each treatment group using a stepwise regression:

$$B_{ij}(\boldsymbol{X}_i, A_i = a) = \text{stepwise}(\text{EMP}_{ij}, \text{MARI}_{ij}, \text{AGE}_{ij}, \text{REL}_{ij}, \text{CAGE}_{ij}, \text{HIV}_{ij}, \text{CDM}_{ij}, \text{X}^1{}_{ij}, \text{X}^2{}_{ij}, \text{X}^3{}_{ij})$$

PS in IPW and DR is fitted for the whole dataset using a stepwise regression:

$$logit(\pi_{ij}(\boldsymbol{X}_i, A_i)) = \text{stepwise}(A_i, \text{EMP}_{ij}, \text{MARI}_{ij}, \text{AGE}_{ij}, \text{REL}_{ij}, \text{CAGE}_{ij}, \text{HIV}_{ij}, \text{CDM}_{ij}, \text{X}^1{}_{ij}, \text{X}^2{}_{ij}, \text{X}^3{}_{ij})$$