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Far from MCAR: Obtaining population-level estimates of HIV viral suppression

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Abstract

Background: Population-level estimates of disease prevalence and control are needed to assess prevention and treatment strategies. However, available data often suffer from differential missingness. For example, population-level HIV viral suppression is the proportion of all HIV-positive persons with suppressed viral replication. Individuals with measured HIV status, and among HIV-positive individuals those with measured viral suppression, likely differ from those without such measurements.

Methods: We discuss three sets of assumptions to identify population-level suppression in the intervention arm of the SEARCH Study (NCT01864603), a community randomized trial in rural Kenya and Uganda (2013–2017). Using data on nearly 100,000 participants, we compare estimates from i) an unadjusted approach assuming data are missing-completely-at-random (MCAR); ii) stratification on age-group, sex, and community; and, iii) targeted maximum likelihood estimation to adjust for a larger set of baseline and time-updated variables.

Results: Despite high measurement coverage, estimates of population-level viral suppression varied by identification assumption. Unadjusted estimates were most optimistic: 50% (95% CI:46–54%) of HIV-positive persons suppressed at baseline, 80% (95% CI:78–82%) at Year 1, 85% (95% CI:83–86%) at Year 2, and 85% (95% CI:83–87%) at Year 3. Stratifying on baseline predictors yielded slightly lower estimates, and full adjustment reduced estimates meaningfully:

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Computing code: Available at <https://github.com/LauraBalzer/Far-From-MCAR>

42% (95%CI:37-46%) of HIV-positive persons suppressed at baseline, 71% (95%CI:69-73%) at Year 1, 76% (95%CI:74-78%) at Year 2, and 79% (95%CI:77-81%) at Year 3.

Conclusions: Estimation of population-level disease burden and control requires appropriate adjustment for missing data. Even in large studies with limited missingness, estimates relying on the MCAR assumption or baseline stratification should be interpreted cautiously.

Keywords

causal inference; HIV viral suppression; machine learning; missing data; Super Learner; TMLE

INTRODUCTION:

Accurate population-level estimates of disease prevalence and treatment coverage are needed to quantify disease burden and evaluate the success of programs for epidemic control. The data available to inform such estimates, however, are often susceptible to differential missingness. In other words, the missing-completely-at-random (MCAR) assumption rarely, if ever, holds.¹⁻⁴ The field of HIV prevention and treatment provides an illustrative example. Consider the UNAIDS 90-90-90 target for the year 2020: 90% of all HIV-positive persons should know their status; 90% of those who know their status should be receiving antiretroviral therapy (ART); and 90% of those receiving ART should have suppressed HIV viral replication.⁵ Multiplying these proportions together yields an overall target, referred to here as “population-level suppression” - 73% of all HIV-positive persons should have suppressed HIV viral replication (Appendix). This target reflects the HIV care “cascade” from diagnosis, through treatment initiation and retention, to viral suppression.

While population-level suppression is widely used in assessing HIV care strategies, two recent systematic reviews noted the variability in both data quality and statistical approaches used for assessment.^{6,7} In particular, Granich *et al.*⁶ remarked on the challenges posed by incomplete data and inconsistent methodology, while Sabapathy *et al.*⁷ proposed a template to standardize data collection and evaluation. In this manuscript, we provide an in-depth demonstration of the methods used to estimate population-level suppression in the SEARCH Study, a cluster randomized trial in rural Kenya and Uganda (NCT01864603).^{8,9} We approach the missing data problem with a causal framework to define target parameters with counterfactuals, state identifiability assumptions sufficient to translate these targets into statistical quantities, and estimate the resulting statistical parameters.^{1-4,10-14} We refer the reader to companion papers for details on the trial.^{8,9}

METHODS:

In general, the total number of HIV-positive persons in a population is unknown, and individuals with known HIV status are not necessarily representative of the general population. If, for example, persons with higher health-seeking behavior are more likely to test and less likely to be infected, then an unadjusted estimate of HIV prevalence (i.e. the proportion with HIV among those tested) is likely to underestimate the true prevalence of HIV in the population, even in the context of community-wide testing, as was implemented in recent Universal-Test-and-Treat trials.^{9,15-18}

Likewise, measurement of plasma HIV RNA levels (viral loads) among HIV-positive individuals is generally incomplete and often depends on factors associated with viral suppression. For example, if viral loads are only measured at HIV clinic visits, then viral suppression among measured individuals will overestimate suppression among all HIV-positive persons, including newly diagnosed individuals who are not yet in-care and previously diagnosed individuals who are out-of-care. These familiar missing data challenges can be illustrated with a directed acyclic graph or another causal modeling approach (Figure 1).^{14,19-24}

Overcoming these challenges requires knowledge of the data generating process. Consider the 16 communities in the intervention arm of the SEARCH Study. After a door-to-door census, we conducted community-wide testing annually through multidisease health fairs, followed by out-of-facility testing for residents who did not attend the fair.^{25,26} We linked participants over successive years with a fingerprint biometric. Prior diagnosis of HIV and ART use were ascertained through linkage to clinic records.^{8,27} A re-census was conducted 3 years after follow-up to determine interim deaths, out-migrations, and in-migrations.⁹

With this measurement scheme in mind, we describe the methods used in Petersen *et al.*⁸ and Havlir *et al.*⁹ to characterize viral suppression in the intervention arm at study baseline $t=0$, and annually thereafter $t=\{1,2,3\}$. These cross-sectional analyses provide snapshots of population-level suppression among an open cohort of adult (>15years) residents (allowing for entry due to age and in-migration, and exit due to death or outmigration). We note estimating viral suppression among a closed cohort of known baseline HIV-positive residents is a distinct goal, resulting in a different causal parameter, identifiability assumptions, and estimation approach.^{8,9}

Causal parameters

Let HIV_t^* be an indicator that an individual is HIV-positive at time t , irrespective of whether serostatus is measured. Likewise, let $Supp_t^*$ be a possibly unmeasured indicator of HIV viral suppression (<500cps/mL) at time t . Population-level suppression is the conditional probability of viral suppression given HIV-positive status: $\mathbb{P}(Supp_t^* = 1 \mid HIV_t^* = 1)$, or equivalently, the joint probability of being HIV-positive with suppression, divided by the probability of being HIV-positive (i.e. HIV prevalence): $\mathbb{P}(Supp_t^* = 1, HIV_t^* = 1) / \mathbb{P}(HIV_t^* = 1)$.

Ideally, anyone not already known to be HIV-positive (i.e. previously HIV-negative or HIV-unknown) would be tested at time t . Of course, this is never the case; further, missingness inherently depends on underlying HIV status - the status of an HIV-negative individual who does not test at time t is unknown, whereas the status of an HIV-positive individual not seen at time t might be known from prior testing. The problem is intensified after multiple rounds of community-wide testing, which provide multiple opportunities for prevalent HIV-positive persons to be diagnosed. To avoid this inherent dependence, we define Δ_t^{HIV} as an indicator that an individual was seen at community-wide testing and had “known” HIV status at time t - due to a negative test result at time t , or a positive result at or before time t . We define observed HIV status as $HIV_t = \Delta_t^{HIV} \times HIV_t^*$.

As with HIV testing, viral load measurement is incomplete; HIV-positive persons on whom viral load is measured may differ systematically from HIV-positive persons who are missing this measure. Define Δ_t^{Supp} as an indicator of viral load measurement at time t , and define observed viral suppression as $Supp_t = \Delta_t^{Supp} \times Supp_t^*$.

Three sets of identifiability assumptions

In the above, population-level suppression was expressed in terms of underlying indicators of HIV seropositivity and viral suppression: $\mathbb{P}(Supp_t^* = 1, HIV_t^* = 1) / \mathbb{P}(HIV_t^* = 1)$. We now present three sets of identifiability assumptions to write the numerator and denominator in this expression as parameters of the observed data distribution (see eAppendix 1 for proofs).

Unadjusted: Suppose we are willing to assume that HIV prevalence among those seen at time t is representative of HIV prevalence among those not seen, and that viral suppression among HIV-positive persons with viral loads measured at time t is representative of suppression among HIV-positive persons without measured viral loads. More formally, suppose we make the following randomization assumptions as applied to missing data: $HIV_t^* \perp \Delta_t^{HIV}$ and $Supp_t^* \perp \Delta_t^{Supp} \mid HIV_t = 1$. If these assumptions hold, the numerator of population-level suppression is identified as

$$\mathbb{P}(Supp_t^* = 1, HIV_t^* = 1) = \mathbb{P}(Supp_t = 1 \mid \Delta_t^{Supp} = 1, HIV_t = 1) \times \mathbb{P}(HIV_t = 1 \mid \Delta_t^{HIV} = 1),$$

and denominator as $\mathbb{P}(HIV_t^* = 1) = \mathbb{P}(HIV_t = 1 \mid \Delta_t^{HIV} = 1)$.²⁷ Taking the ratio of these yields the unadjusted statistical parameter:

$$\mathbb{P}(Supp_t = 1 \mid \Delta_t^{Supp} = 1, HIV_t = 1). \quad (\text{Eq1})$$

Baseline adjustment: We can weaken the above assumptions on the missingness process by conditioning on baseline covariates. Specifically, let B denote mutually exclusive and exhaustive strata defined by age group, sex, and community of residence. Now suppose within each strata b , HIV prevalence among those seen at time t is representative of prevalence among those not seen, and within each strata b , suppression among HIV-positive persons with viral loads measured at time t is representative of suppression among HIV-positive persons without measured viral loads. More formally, we assume $HIV_t^* \perp \Delta_t^{HIV} \mid B$ and $Supp_t^* \perp \Delta_t^{Supp} \mid HIV_t = 1, B$.

Under these assumptions on missingness, we obtain the following identifiability result, corresponding to a hypothetical, dynamic intervention to first ensure knowledge of HIV status and then to ensure measurement of viral loads among HIV-positive persons:²⁸⁻³¹

$$\begin{aligned}
 & \mathbb{P}(Supp_t^* = 1, HIV_t^* = 1) \\
 = & \sum_b \mathbb{P}(Supp_t = 1 \mid \Delta_t^{Supp} = 1, HIV_t = 1, B = b) \times \mathbb{P}(HIV_t = 1 \mid \Delta_t^{HIV} = 1, B = b) \times \mathbb{P}(B = b) \quad (\text{Eq2}) \\
 = & \mathbb{P}(Supp_t = 1 \mid \Delta_t^{Supp} = 1, HIV_t = 1, B = b) \times \mathbb{P}(HIV_t = 1 \mid \Delta_t^{HIV} = 1, B = b) \times \mathbb{P}(B = b)
 \end{aligned}$$

In words, this is the strata-specific probability of viral suppression, given measurement and HIV-positive status; multiplied by the strata-specific probability of being HIV-positive, given measurement; and then standardized with respect to the distribution of strata. Identification of the denominator, population-level prevalence, follows from above:

$$\mathbb{P}(HIV_t^* = 1) = \sum_b \mathbb{P}(HIV_t = 1 \mid \Delta_t^{HIV} = 1, B = b) \times \mathbb{P}(B = b) \quad (\text{Eq3})$$

By taking the ratio of the numerator (Eq2) to the denominator (Eq3), we obtain a baseline-adjusted statistical parameter corresponding to population-level suppression under the above assumptions.

For the conditioning sets to be well defined, we also require the positivity assumption.^{11,32} Irrespective of age, sex, and community, there must be a positive probability of being seen with known HIV status $\mathbb{P}(\Delta_t^{HIV} = 1 \mid B) > 0$, and for every strata in which some proportion of HIV-positive persons are seen, there must be a positive probability of viral load measurement: $\mathbb{P}(\Delta_t^{Supp} = 1 \mid HIV_t = 1, B) > 0$.

Time-varying adjustment: While stratifying on certain baseline characteristics weakens our assumptions on missingness, there may be many other variables potentially impacting testing, underlying HIV status, and viral suppression among HIV-positive persons. In particular, ART use is a key determinant of viral suppression and may also be predictive of viral load measurement.

Define ART_t as an indicator of ART initiation prior to time t , and let X_t denote the remaining observed variables that are potentially predictive of both viral suppression and its measurement: the full set of baseline demographics (e.g. age, sex, marital status, education, occupation, alcohol use, mobility, wealth index, and community) together with prior HIV testing and suppression. While viral suppression without ART is possible, the UNAIDS target is focused on ART-induced suppression (Appendix).⁵ Therefore, we set $Supp_t^*$ to zero for persons not on ART. We further assume complete measurement of ART use, acknowledging that if ART use is incompletely captured, this assumption will lead to underestimation of suppression. Finally, for HIV-positive persons who have initiated ART, we assume that conditional on baseline and time-updated covariates X_b , suppression among those with a measured viral load at time t is representative of suppression among those with a missing viral load. More formally, we assume $Supp_t^* \perp \Delta_t^{Supp} \mid ART_t = 1, X_t$.

We also require the positivity assumption; all HIV-positive individuals who have initiated ART have a positive probability of having their viral load measured, regardless of their

baseline and time-updated covariates: $\mathbb{P}(\Delta_t^{Supp} = 1 \mid ART_t = 1, X_t) > 0$ a.e.. Under these assumptions, we have the following identifiability result corresponding to a hypothetical intervention to ensure viral load measurement among ART initiators:²⁸

$$\begin{aligned} & \mathbb{P}(Supp_t^* = 1, HIV_t^* = 1) \\ &= \mathbb{P}(ART_t = 1) \times \sum_{x_t} \mathbb{P}(Supp_t = 1 \mid \Delta_t^{Supp} = 1, ART_t = 1, X_t = x_t) \times \mathbb{P}(X_t = x_t \mid ART_t = 1) \end{aligned} \quad (\text{Eq4})$$

where the summation generalizes to an integral for continuous covariates. In words, this is the proportion of individuals who have started ART (and are, by implication, HIV-positive) in the total population (including both HIV-positive and HIV-negative persons) multiplied by the adjusted probability of being suppressed, given prior ART initiation.

For the denominator of HIV prevalence, we also consider an expanded adjustment set L_t , consisting of all baseline demographics and prior HIV testing. For the subgroup without a prior HIV diagnosis, we assume that conditional on L_t , HIV prevalence among those tested at time t is representative of HIV prevalence among those not tested, or more formally, $HIV_t^* \perp \Delta_t^{HIV} \mid L_t, HIV_{t-1} = 0$. We further assume positivity; previously undiagnosed persons have some chance of being tested regardless of their L_t values:

$\mathbb{P}(\Delta_t^{HIV} = 1 \mid HIV_{t-1} = 0, L_t) > 0$ a.e.. Under these assumptions, we have the following identifiability result corresponding to a hypothetical intervention to ensure HIV status is known:²⁸

$$\begin{aligned} & \mathbb{P}(HIV_t^* = 1) = \mathbb{P}(HIV_{t-1} = 1) + \\ & \quad \mathbb{P}(HIV_{t-1} = 0) \times \sum_{l_t} \mathbb{P}(HIV_t = 1 \mid \Delta_t^{HIV} = 1, L_t = l_t, HIV_{t-1} = 0) \\ & \quad \times \mathbb{P}(L_t = l_t \mid HIV_{t-1} = 0) \end{aligned} \quad (\text{Eq5})$$

where the summation generalizes to an integral for continuous covariates. In words, this is the proportion of the population previously known to be HIV-positive plus the adjusted proportion of the population newly known to be HIV-positive.

Taking the ratio of the numerator (Eq4) to the denominator (Eq5) yields a fully adjusted statistical parameter for population-level suppression under the above assumptions.

Estimation approaches

The unadjusted parameter (Eq1) can be estimated with the empirical proportion of the population with measured viral suppression. The baseline-adjusted parameter (Eq2÷Eq3) can also be estimated with empirical proportions. Specifically, we would generate covariate strata-specific estimates by taking empirical means, and then combine by standardizing across strata. A similar approach was used in the PopART (HPTN 071) Universal-Test-and-Treat trial with stratification factors including sex, age group and community.^{17,33,34} This approach corresponds to G-computation when fully-saturated regressions are used to estimate the conditional probability of the outcome, given measurement and the adjustment set (i.e. the “outcome regression”).^{28,35,36} It is further equivalent to inverse-weighting when

fully-saturated regressions are used to estimate the conditional probability of measurement, given the adjustment set (i.e. the “propensity score”).³⁷⁻³⁹

When the adjustment set is higher dimensional, such as for our fully-adjusted parameter (Eq4÷Eq5), alternative approaches are needed to smooth over values of the covariates with weak support.³² We could, for example, use logistic regression with two-way interactions to estimate the propensity scores for inverse-weighting. This approach was used in a sensitivity analysis in the Ya Tsie Universal-Test-and-Treat trial (also called the Botswana Combination Prevention Project).^{18,40}

Another approach is targeted maximum likelihood estimation (TMLE), which offers efficiency gains over inverse-weighting and allows for flexible adjustment for a large set of covariates through machine learning.^{24,41} We refer the reader to ^{42,43} for an introduction to TMLE and to ⁴⁴ for a detailed comparison with other methods, such as parametric G-computation and augmented inverse-weighting. Briefly, TMLE combines estimates of outcome regression with estimates of the propensity score to achieve a number of desirable properties. TMLE is double robust - it is consistent if either the outcome regression is consistently estimated or the propensity score is consistently estimated. TMLE is also a substitution estimator, potentially improving robustness under strong confounding or rare outcomes.⁴⁴⁻⁴⁷

In eAppendix 2, we provide step-by-step descriptions of the unadjusted estimator, parametric G-computation, inverse-weighting estimator, and TMLE to adjust for missing outcomes.

Implementation

In the SEARCH Study, the primary approach used TMLE to estimate the fully adjusted parameter (Eq4÷Eq5). Within TMLE, Super Learner was implemented to estimate the outcome regressions and propensity scores (i.e. the conditional probability of measurement, given the adjustment set).⁴⁸ Super Learner is an ensemble, machine learning method that uses cross-validation to build the optimal combination of predictions from a library of candidate algorithms. For ease of interpretation, reduced computational burden, and to avoid over-fitting, our Super Learner library was limited to logistic regressions (with various screening algorithms), generalized additive models (with various screening algorithms), and the mean (corresponding to the unadjusted estimator). We implemented TMLE fully stratified on community, allowing the outcome regressions and propensity scores to vary by community. Full implementation details, including computing code, are available in eAppendix 3.

For comparison, we also present the use of empirical proportions to estimate the unadjusted parameter (Eq1), and the baseline-adjusted parameters (Eq2÷Eq3) controlling for sex, age group (15-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, and 60+ years), and community.

We obtained statistical inference with influence curve standard errors, treating the community as the unit of independence. We conducted analyses in R v.3.6.1 (Vienna, Austria) with the `ltmle_v1.1.1-0` and `SuperLearner_v2.0-25` packages.⁴⁹⁻⁵¹

Ethical considerations

The SEARCH Study was approved by the ethics committees at the University of California, San Francisco; the Kenya Medical Research Institute; and Makerere University School of Medicine in Uganda. As previously described,⁹ oral informed consent was provided participation in the census and health fairs; written informed consent was provided to receive ART outside of country guidelines.

RESULTS

The baseline characteristics of the study participants have been described elsewhere.^{8,9,25} In brief, approximately one-third of the 79,818 residents enumerated in the baseline census were from each study region, and nearly half of participants were aged 15-30 years; men constituted 45% (eTable 1). HIV status was determined on 89% (71,402) of residents at baseline (Table 1). After baseline, knowledge of HIV serostatus remained high with 77% of residents (69,175/90,047) seen at Year 1, 75% (71,577/95,599) at Year 2, and 81% (80,390/99,186) at Year 3. There were no obvious demographic differences between the enumerated population and those with known HIV serostatus (eTable 1).

Viral loads were measured for 76% of baseline HIV-positive residents (Table 1). Missing viral loads were more common at baseline due to early assay failures.²⁶ Despite ~95% coverage of viral load measurement for the remaining years, baseline and time-varying characteristics differed for HIV-positive persons with measured versus missed HIV RNA levels (Table 2). In particular, HIV-positive women were more likely to have their viral load measured than HIV-positive men. After baseline, adolescents (15-24years) were more likely to be missed than older adults (25+years). Viral load measurement also differed notably by the time-varying characteristics; HIV-positive persons who were previously aware of their status, had evidence of starting ART, or had a history of suppressing viral replication were more likely to have their viral load measured than their counterparts.

Estimates of population-level suppression varied meaningfully depending on the identifiability assumptions employed (Figure 2). At baseline, the unadjusted approach suggested that half of all HIV-positive residents had suppressed viral replication (50%; 95% CI: 46-54%). Stratifying on age group, sex, and community slightly reduced the estimate to 49% (95% CI: 45-54%). The lowest estimate of 42% (95% CI: 37-46%) was obtained after adjusting for the full set of baseline and time-varying characteristics.

Deviations were pronounced in subsequent years (Figure 2). The unadjusted approach suggested that 80% (95% CI: 78-82%) of all HIV-positive residents were suppressed at Year 1, 85% (95% CI: 83-86%) at Year 2, and 85% (95% CI: 83-87%) at Year 3. Estimates adjusted for baseline covariate-strata were similar: 79% (95% CI: 77-81%) at Year 1, 84% (95% CI: 82-86%) at Year 2, and 84% (95% CI: 83-86%) at Year 3. Fully adjusted estimates

were meaningfully lower: 71% (95%CI: 69-73%) at Year 1, 76% (95%CI: 74-78%) at Year 2, and 79% (95%CI: 77-81%) at Year 3.

DISCUSSION:

In an open cohort of nearly 100,000 residents in rural Kenya and Uganda, we compared three approaches for missing outcomes: (i) an unadjusted approach, the empirical proportion among those measured; (ii) stratification on age group, sex, and community; and (iii) TMLE with Super Learner to adjust for the full set of baseline and time-varying covariates. Despite low levels of missingness, estimates diverged by identifiability assumptions. The unadjusted approach consistently yielded the highest estimates; the fully adjusted approach consistently yielded the lowest estimates.

In the SEARCH Study, HIV serostatus and HIV RNA viral levels were obtained through multidisease testing at health fairs with follow-up for non-participants.²⁵ Unlike clinic-based ascertainment, this approach reaches HIV-positive persons who are in-care or who are out-of-care.^{9,16-18} As a result, the MCAR assumption may seem reasonable.¹⁻⁴ However, deviations between the unadjusted estimates and adjusted ones suggest there were meaningful differences in the population measured and population missed with respect to, among other factors, prior diagnosis, ART use, and viral suppression.

Both adjusted approaches were built on causal assumptions that (distinct subsets of) observed participant characteristics were sufficient to control for the common causes of measurement and health outcomes.¹⁻⁴ When assuming baseline covariates were sufficient, we fully stratified on sex, age group, and community; as a result, this was equivalent to a fully non-parametric approach for the outcome regression in G-computation and to a fully non-parametric approach for the propensity score in inverse-weighting. Beyond age, sex, and community, there were, however, additional differences between those with measured versus missing viral loads, including differences in post-baseline variables; specifically, persons without prior diagnosis, ART initiation, or viral suppression were less likely to have their viral load measured. Therefore, the primary approach in the SEARCH Study was to weaken the assumptions on the missingness process by conditioning on a larger set of baseline and time-updated covariates.^{8,9,27} We estimated the fully adjusted statistical parameter using TMLE with Super Learner.

It is important to note, however, that the primary approach still relied on non-testable assumptions. If there is an unmeasured cause of measurement and health outcomes, none of the identifiability assumptions will hold and the wished-for causal parameters will diverge from the statistical estimands. In the SEARCH Study, we aimed to minimize this divergence by conditioning on a large set of baseline and time-varying variables and assessing the plausibility of assumptions with experts in HIV prevention. During estimation, we further aimed to avoid unsubstantiated assumptions and minimize bias due to model misspecification by using TMLE with Super Learner. This approach will provide a consistent point estimate if either the outcome regression or the propensity score is consistently estimated and will provide consistent inference (i.e. valid confidence intervals) when both are consistently estimated at sufficiently fast rates and satisfy the relevant

empirical process conditions.^{52,53} Recent extensions to obtain double robust inference, while of interest, were not implemented in the current analyses.

While it is well recognized that estimates can only be interpreted causally if the identifiability assumptions hold, similar challenges apply when interpreting estimates adjusting for missing data.¹⁴ Specifically, our estimates are only truly representative of population-level metrics if the missingness assumptions hold¹³ and there is sufficient data support. These challenges, however, should not inspire inaction; instead, we often need to use available data to obtain timely estimates of disease burden and control under minimal assumptions, which are transparently stated and carefully evaluated.

In the running example, the identification choice had implications for policymaking and targeting resources. Both the unadjusted and baseline-adjusted approaches suggested the UNAIDS 90-90-90 target (73%-suppression) was surpassed within one year of the intervention and the UNAIDS 95-95-95 target (86%-suppression) was nearly achieved by the trial's close.⁵ In contrast, the estimates controlling for time-updated covariates indicated the 90-90-90 target was achieved after two years, but there still was a substantial gap to the 95-95-95 target.

In summary, estimates of population-level HIV viral suppression continue to be the benchmark in assessing programmatic success in epidemic control. In four cross-sectional analyses of nearly 100,000 participants in the intervention arm of the SEARCH Study, we demonstrated the impact of missing data assumptions that can occur even in large studies with high measurement. While we focused on a specific example – estimating population-level HIV viral suppression – our results have broad applicability to missing data problems, commonly encountered in public health and medicine.^{3,4,10-13} We recommend adjustment for a large set of baseline and time-varying covariates that potentially influence both measurement and underlying status; TMLE with Super Learner is one approach to performing such adjustments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability:

Data sufficient to reproduce the study findings will be made available approximately one year after completion of the ongoing trial (NCT01864603). Further inquiries can be directed to the SEARCH Scientific Committee at douglas.black@uscf.edu.

Appendix:: UNAIDS 90-90-90 target and population-level suppression

For the moment assume complete measurement, and let HIV_t be an indicator of HIV-positive serostatus at time t , Dx_t be an indicator of having an HIV diagnosis by time t , ART_t be an indicator of antiretroviral therapy (ART) use at time t , and $Supp_t$ be an indicator of suppressed viral replication at time t . The UNAIDS 90-90-90 targets are a series of proportions or conditional probabilities:⁵

% of all HIV-positives who are diagnosed (first-90):

$$\mathbb{P}(Dx_t = 1 \mid HIV_t = 1) = \frac{\mathbb{P}(Dx_t = 1, HIV_t = 1)}{\mathbb{P}(HIV_t = 1)}$$

% of diagnosed who are on ART (second-90):

$$\mathbb{P}(ART_t = 1 \mid Dx_t = 1, HIV_t = 1) = \frac{\mathbb{P}(ART_t = 1, Dx_t = 1, HIV_t = 1)}{\mathbb{P}(Dx_t = 1, HIV_t = 1)}$$

% on ART who are currently suppressed (third-90):

$$\mathbb{P}(Supp_t = 1 \mid ART_t = 1, Dx_t = 1, HIV_t = 1) = \frac{\mathbb{P}(Supp_t = 1, ART_t = 1, Dx_t = 1, HIV_t = 1)}{\mathbb{P}(ART_t = 1, Dx_t = 1, HIV_t = 1)}$$

Multiplying together the three “90s” yields the proportion of all HIV-positive persons who are currently suppressed (i.e. population-level suppression):

$$\mathbb{P}(Supp_t = 1 \mid HIV_t = 1) = \frac{\mathbb{P}(Supp_t = 1, ART_t = 1, Dx_t = 1, HIV_t = 1)}{\mathbb{P}(HIV_t = 1)}$$

Since each numerator and denominator is a population-level proportion, we can equivalently express the targets as follows: first-90=(number previously diagnosed)/(number HIV-positive), second-90=(number on ART)/(number previously diagnosed), third-90=(number virally suppressed)/(number on ART), and population-level suppression=(number virally suppressed)/(number HIV-positive).

Therefore, one could directly estimate population-level suppression, as we demonstrated here, or instead estimate each 90-90-90 target and multiply. These two approaches should yield identical results, as demonstrated in our previous work.^{8,9,27} However, deviations between the direct estimate and the multiplied-one can occur when making the missing-completely-at-random (MCAR) assumption.¹⁻⁴ Specifically, under MCAR, the denominators of the third-90 and population-level suppression become conditional on having a viral load measured, which is almost always a subset of the population on ART and a subset of the population who is HIV-positive.

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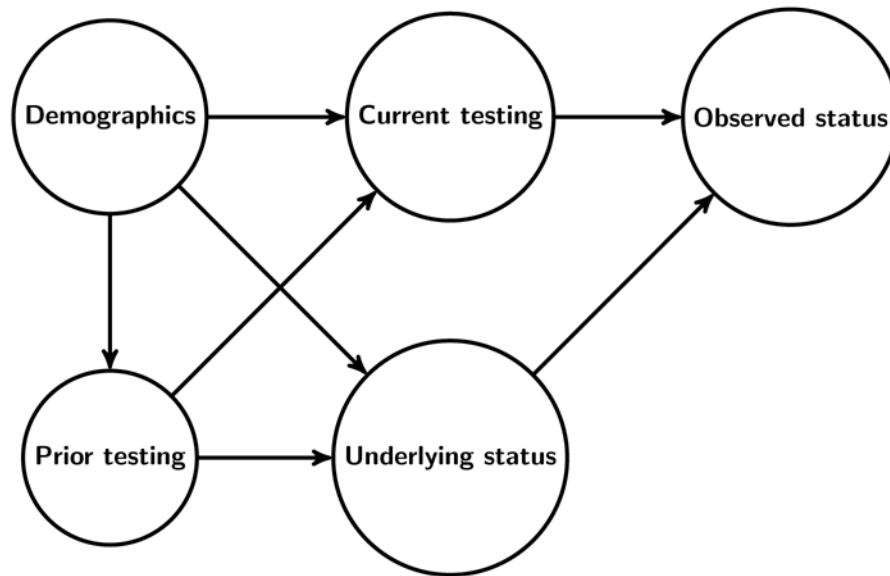


Figure 1: Simplified directed acyclic graph to represent the challenges posed by incomplete HIV testing. Demographics and prior testing are common causes of current testing (the hypothetical intervention node) and underlying HIV status (possible unobserved), both of which impact observed HIV status. Analogous challenges arise due to incomplete measurement of suppression among HIV-positive persons.

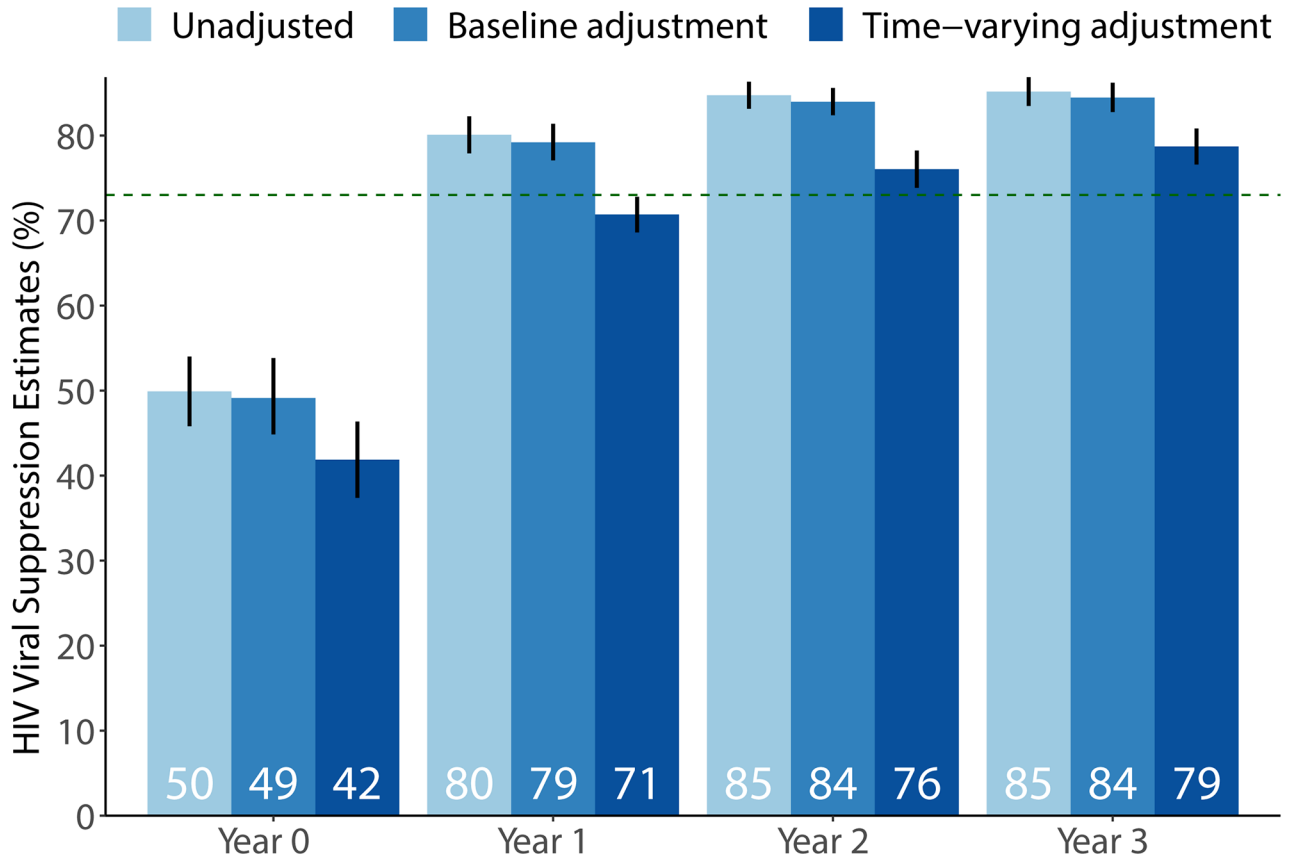


Figure 2: Estimates of population-level HIV viral suppression at the time of annual testing in the intervention arm of the SEARCH trial. Estimates were obtained with the empirical mean among those measured (“Unadjusted”), stratifying on sex, age group and community (“Baseline adjustment”), and using targeted maximum likelihood estimation (TMLE) with Super Learner to adjust for both baseline and time-varying characteristics (“Time-varying adjustment”). Horizontal dashed line at 73% suppression indicates UNAIDS target; vertical lines indicate 95% confidence intervals.

Table 1:

Number and coverage of residents contributing to unadjusted estimates of population-level HIV viral suppression at the time of annual testing. Each column is a subset of the former. Changes in annual population size are due to additions from in-migrants and aging-in, and due to subtractions from death and outmigration. Years refer to time since study baseline, which varied by community (Year 0 ranging from June 2013 to June 2014).

	Resident (> 15 years)	HIV serostatus known	HIV-positive serostatus	Viral load measured	Viral replication suppressed
Year 0	79818	71402	7009	5332	2659
Year 1	90047	69175	6526	6137	4906
Year 2	95599	71577	6687	6276	5316
Year 3	99186	80390	6991	6738	5737

Table 2:

Select baseline and time-varying characteristics of HIV-positive residents by year and by viral load measurement. Metrics in N (%).

	Total	Female	Male	15-24 years	25+ years	Prior diagnosis ^a	Prior ART use ^b	Prior Supp. ^c
Year 0								
Tested	5332	3599 (67)	1733 (33)	687 (13)	4645 (87)	3856 (72)	3149 (59)	
Missed	1677	1060 (63)	617 (37)	226 (13)	1451 (87)	1081 (64)	847 (51)	
Year 1								
Tested	6137	4100 (67)	2037 (33)	729 (12)	5408 (88)	5917 (96)	5591 (91)	2276 (37)
Missed	389	238 (61)	151 (39)	54 (14)	335 (86)	310 (80)	225 (58)	92 (24)
Year 2								
Tested	6276	4168 (66)	2108 (34)	782 (12)	5494 (88)	6153 (98)	5970 (95)	4637 (74)
Missed	411	247 (60)	164 (40)	89 (22)	322 (78)	333 (81)	230 (56)	141 (34)
Year 3								
Tested	6738	4603 (68)	2135 (32)	1023 (15)	5715 (85)	6480 (96)	6376 (95)	5108 (76)
Missed	253	135 (53)	118 (47)	54 (21)	199 (79)	222 (88)	173 (68)	143 (57)

Abbreviations: “ART”=antiretroviral therapy; “Supp”=Suppression.

^aPositive HIV test or Ministry of Health record of HIV care before the start of the community-specific health fair at year *t*.

^bART use, as determined through Ministry of Health records or suppressed HIV RNA, before the start of the community-specific health fair at year *t*.

^cSuppressed HIV RNA before the start of the community-specific health fair at year *t*.