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# Predicting HIV Incidence in the SEARCH Trial: A Mathematical Modeling Study

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## Abstract

**Background:** The SEARCH study provided community-based HIV and multi-disease testing and antiretroviral therapy (ART) to 32 communities in East Africa and reported no statistically significant difference in three-year HIV incidence. We used mathematical modelling to estimate the effect of control arm viral suppression and community mixing on SEARCH trial outcomes.

**Setting:** Uganda and Kenya.

**Methods:** Using the individual-based HIV modeling software EMOD-HIV, we configured a new model of SEARCH communities. The model was parameterized using demographic, HIV prevalence, male circumcision, and viral suppression data, and calibrated to HIV prevalence, ART coverage, and population size. Using assumptions about ART scale-up in the control arm, degree of community mixing, and effect of baseline testing, we estimated comparative HIV incidence under multiple scenarios.

**Results:** Prior to the trial results, we predicted that SEARCH would report a 4-40% reduction between arms, depending on control arm ART linkage rates and community mixing. With universal baseline testing followed by rapidly expanded ART eligibility and uptake, modelled effect sizes were smaller than the study was powered to detect. Using interim viral suppression data, we estimated three-year cumulative incidence would have been reduced by up to 27% in the control arm and 43% in the intervention arm compared to a counterfactual without universal baseline testing.

**Conclusions:** Our model suggests that the active control arm substantially reduced expected effect size and power of the SEARCH study. However, compared to a counterfactual "true control" without increased ART linkage due to baseline testing, SEARCH reduced HIV incidence by up to 43%.

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**Keywords**

mathematical modeling; HIV prevention; treatment-as-prevention; incidence estimation; East Africa

## INTRODUCTION

Mathematical modeling is a key tool for understanding epidemics and estimating the effect of interventions on incidence reduction. However, the usefulness of models hinges on their ability to characterize transmission patterns and predict incidence accurately. Using a previously developed individual-based model of HIV transmission – EMOD-HIV – we had the opportunity to evaluate the ability of the model to predict HIV incidence in the context of the Sustainable East Africa Research in Community Health (SEARCH) study, prior to the availability of measured outcome data.

The SEARCH study (NCT01864683) is one of four major randomized-controlled trials (RCTs) that investigated a strategy of community-based treatment-as-prevention (TasP) for reduction of HIV incidence in sub-Saharan Africa.[1] SEARCH is based in 32 rural communities of approximately 10,000 people each in three regions of East Africa – Eastern Uganda, Western Uganda, and Western Kenya. Eastern Uganda communities are characterized by average HIV prevalence among adults of 4%, while in Western Ugandan and Kenyan communities, adult prevalence averages 7% and 19%, respectively.[2] The study, which took place from 2013 to 2017, investigated the effect of universal HIV treatment and streamlined care on HIV incidence, mortality, and non-communicable disease control, among other health and economic outcomes.

Prior to baseline data collection, a census was conducted in each of the 32 communities to enumerate all individuals in study communities. At baseline (2013-2014), two-week community-wide testing campaigns (CHCs) were conducted in all control and intervention arm communities. At each CHC, all participants were offered multi-disease services, including screening and treatment for HIV, hypertension, diabetes, and malaria, as well as deworming for children. Residents who did not attend a CHC were contacted and offered home-based testing (HBT) in their residence or other location of choice. Through a combination of CHCs and HBT, SEARCH achieved 89% baseline testing coverage across both arms of the trial at baseline.[3] HIV incidence was measured in a population-level cohort of HIV-negative resident adults ≥15 years old at baseline, and 3-year cumulative HIV incidence in this cohort was the primary study endpoint.

In the control arm, individuals were offered standard-of-care ART initiation according to national guidelines. Over the three years of study follow-up, guidelines for the general population changed from CD4 counts ≤350 cells/μl to CD4 counts ≤500 cells/μl in Kenya and Uganda in July 2014 and December 2013, respectively.[4,5] Both countries also adopted guideline changes for universal test-and-treat in July 2016 (Kenya)[6] and November 2016 (Uganda).[7] Changes in ART eligibility were rapidly implemented in clinics in the control communities [8]. In the intervention arm, HIV-positive individuals were offered immediate and universal ART, regardless of CD4 count or other criteria, along with annual testing

campaigns and streamlined care interventions (e.g. same-day ART start and 3-monthly refills).[9] At baseline, 45% of HIV-positive, stable adult residents (i.e., those residing in the community for ≥ six months out of the year) were virally suppressed; population-level suppression increased to 80% in the intervention arm of the study after two years of the intervention, exceeding the UNAIDS 90-90-90 targets.[10]

Although ART is proven to reduce transmission on an individual level, the magnitude of the impact of universal test-and-treat implemented at a community level on HIV incidence depends on multiple factors, including 1) the extent to which testing in the context of universal eligibility results in increased population-level suppression, and 2) the contributions of sexual relations outside the community to new infections. SEARCH communities were not geographically isolated and mobility has also been associated with increased risk of HIV acquisition for both men and women.[11-13] Furthermore, in the SEARCH study, universal baseline testing was conducted in both arms in order to isolate the effects of ART eligibility and the care delivery model; the impact of baseline testing on subsequent linkage and suppression among HIV+ individuals in the control arm, particularly in the context of the rapidly expanded ART eligibility that occurred during the trial, could substantially reduce the expected difference in HIV incidence between arms, and thus the statistical power to detect a difference.

Data on interim viral suppression in the control arm and exposure to individuals outside of SEARCH communities were not measured. However, by the end of year 3, population-level viral suppression among all HIV+ individuals, including in-migrants, was 11% higher in the intervention arm compared to the control arm (79% and 68%, respectively).[8] The study found no significant difference in HIV incidence, with a relative risk (RR) of 0.95, (95% confidence interval [CI]: 0.77-1.17), although annual incidence in the intervention arm declined by 32% from year 1 to year 3 (relative rate 0.68, 95% CI: 0.56-0.84).[8]

In this analysis, we used an individual-based mathematical model of the SEARCH study to provide additional context throughout and after Phase I of the trial. Our aims were to estimate anticipated HIV incidence and relative risk between the intervention and control arms, prior to the release of trial results, to validate the model, and to investigate questions not possible to ask with trial data alone. Modelers conducting the study were formally blinded to SEARCH incidence results, allowing the analysis to serve as a prospective test of model validity and to infer potential reasons for the trial outcome that would be consistent with other observations made throughout the trial. A preprint of model results was published simultaneously with the presentation of trial results.[14] We further used the model to estimate the likely impact of the interventions delivered in each arm of the trial relative to a counterfactual “true control” with no SEARCH activities.

## METHODS

We used an existing individual-based model of HIV transmission, EMOD-HIV, to configure a new version of the model encompassing the 32 SEARCH communities in Uganda and Kenya. The model is publicly available (https://github.com/InstituteForDiseaseModeling/EMOD) and has been described previously[15-20]; briefly, it is a stochastic, individual-based

network model of heterosexual and vertical HIV transmission that includes age-specific fertility, age- and sex-specific mortality, four types of heterosexual relationships – commercial, transitory, informal, and marital – with age-specific partnership formation, and a time-varying HIV care cascade encompassing different modes of testing, diagnosis, and linkage to treatment. Further detail about model structure, input, and calibration is available in Supplementary Appendix S1.

In the model, the 32 SEARCH communities were categorized into six nodes – three for each arm of the trial – using k-means clustering based on community HIV prevalence at baseline, population age structure, mobility (≥1 day of travel in the prior month), and male circumcision prevalence.[21] For simplicity, we refer to these nodes as "Control: High Prevalence", "Control: Medium Prevalence", "Control: Low Prevalence", "Intervention: High Prevalence, "Intervention: Medium Prevalence", and "Intervention: Low Prevalence" due to prevalence being the key defining difference in the clusters (Figure 1A).

The model was parameterized using demographic, HIV prevalence, and viral suppression data from the baseline of the SEARCH study at the midpoint of 2013.[2] In the intervention arm nodes of the model, ART scale-up was modelled using viral suppression data from follow-up years 1 and 2, with subsequent incorporation of year 3 data. The model was calibrated to a set of parameters including base infectivity, proportion of low-risk individuals by node, risk assortativity, number of potential external partners by risk, condom use, and ART linkage probability. A full list is available in the supplementary appendix (Table S2). Model calibration figures, showing 250 best-fit trajectories for node-specific HIV prevalence over time and age-specific HIV prevalence at baseline, are shown in Figure 1B. Modelers conducting the study were formally blinded to all data on incident HIV in the study.

Prior to collection of data in year 3, we simulated four scenarios across the two greatest sources of uncertainty: ART scale-up in the control arm and external mixing of SEARCH residents with non-SEARCH community members that were not receiving the interventions (Table 1, scenarios A-D). External mixing is assumed to range from a minimum of 0% mixing (i.e., communities are closed cohorts) to a maximum of 50% mixing, a scenario in which SEARCH residents have an equal probability of mixing with a non-SEARCH individual as they do with another SEARCH resident. ART scale-up in the control arm is assumed to depend on the degree to which the baseline testing campaigns resulted in additional linkage to care. We examined scenarios in which baseline testing in the control arm did not increase linkage, resulting in a projected 69% of baseline HIV-infected individuals in the control communities virally suppressed by the end year 3, and in which baseline testing substantially increased linkage to care, resulting in a maximum of 76% of baseline HIV-infected individuals virally suppressed by year 3.

In the model, all HIV-negative adults aged ≥15 years old compose the incidence cohort at baseline and three-year cumulative incidence is calculated within this cohort. Relative risk and 90% uncertainty intervals (UI) for each scenario across repetitions are reported using the mean number of infected and uninfected individuals in the modelled control and intervention arms, across all 250 best-fit parameter sets. A two-sided t-test at a 5% level of significance

was used to compare differences in three-year cumulative incidence in the modelled control and intervention arms across multiple repetitions of the experiment.

We simulated three additional scenarios informed by the cascade of care and year 3 viral suppression data (scenarios E-G, respectively, in Table 1). First, in order to quantify the impact of SEARCH testing and treatment in both arms relative to a counterfactual "true control," we estimated HIV incidence with no baseline testing in either arm but including male circumcision and guideline changes over time. Second, we estimated incidence in both arms incorporating year 3 viral suppression data and estimating the prevalence of external mixing using node-specific mobility data from study baseline (i.e., the proportion of stable adult residents spending at least one night away from home in the prior month); this "precision estimate" served as a means to evaluate the ability of the model to accurately predict incidence. Lastly, we estimated HIV incidence in both arms using year 3 viral suppression data (as in the precision estimate), but in the absence of external mixing, providing insight into the potential impact of a test-and-treat strategy deployed on a regional or country (rather than community) level.

## RESULTS

### Projections of HIV Incidence Prior to Trial Results

We first projected HIV incidence in the intervention and control arms under a range of hypothetical scenarios. In the "closed cohort" scenario of no external mixing and no additional ART linkage in the control arm (Figure 2A), mean cumulative 3-year incidence in the control arm, averaged across all simulations, was 1.73% compared to 1.04% in the intervention arm. The mean effect size between the intervention and control arms, across all simulations, was a 40% reduction in cumulative 3-year incidence (90% UI: 33%, 46%). In the second scenario (Figure 2B) – a closed cohort but with maximum ART linkage in the control arm – the mean reduction was 14% with 95% of simulations falling between a 3-23% reduction in incidence. In the third scenario with equivalent mixing between SEARCH and non-SEARCH community members, but no additional ART linkage in the control arm (Figure 2C), cumulative 3-year incidence was reduced by a mean of 17%, with 95% of the simulations showing between a 8%-24% reduction. Finally, if equivalent external mixing and additional ART linkage in the control arm occurred together (Figure 2D), the mean reduction in cumulative 3-year incidence was 4%, and 95% of simulations showed between a −6-13% reduction. Across all permutations of external mixing and ART linkage in the control arm, we estimated that the true effectiveness of the SEARCH study would be between a 4-40% reduction in new infections, even if the trial did not report a statistically significant result.

### Estimation of Modeled True Effect Size

Second, we evaluated likely true effect sizes in the SEARCH study based on post-baseline data on viral suppression and baseline data on mobility. Figure 3, Scenario F shows a "precision estimate" based on incorporating year 3 viral suppression data, in both control and intervention arms, and a proxy for external mixing using baseline mobility data. Annual incidence in the intervention arm was predicted to decline from 0.68/100 PY (90% UI: 0.59,

0.75) at year 1 to 0.39/100 PY (90% UI: 0.34, 0.43) by year 3, and from 0.67/100 PY (90% UI: 0.60, 0.76) in the control arm at year 1 to 0.46/100 PY (90% UI: 0.40, 0.51) by year 3, resulting in a predicted cumulative incidence of 1.0% in the intervention arm and 1.2% in the control arm, with a mean true relative effect size of 10% (mean RR 0.90, 90% UI: 0.81, 1.00).

### HIV Incidence Reduction in Comparison to a "True Control"

Third, we estimated the magnitude of impact on HIV incidence of the interventions in each of the SEARCH arms relative to a counterfactual "true control" in which HIV incidence was projected in all 32 SEARCH communities in the absence of SEARCH testing or treatment activities. This scenario is intended to represent HIV incidence in the same communities if the trial had not taken place but allows for expanded ART eligibility according to national guidelines, as well as background levels of testing, VMMC scale-up, and linkage to care (Figure 3, Scenario E). In this modelled "true control" arm, incidence declined from 0.75/100 PY (90% UI: 0.66, 0.84) to 0.70/100 PY (90% UI: 0.61, 0.78) from years 1 to 3 of the trial due to scale-up of male circumcision and expanded ART eligibility in the normal cascade of care. Due to slightly higher HIV prevalence in the intervention arm of the trial at baseline (10.2% versus 10.0% in the control arm), counterfactual three-year cumulative incidence was estimated to be 1.78% in communities that were randomized to the control arm, and 1.83% in communities randomized to the intervention arm. We compared this incidence to both intervention and control arm incidence, including year 3 viral suppression data from the trial. We thus estimated that 3-year cumulative HIV incidence would have been reduced by 27% (90% UI: 20%, 34%) in the SEARCH intervention arm and by 17% (90% UI: 9%, 25%) relative to a modelled counterfactual "true control" arm in which no SEARCH activities occurred.

Finally, in order to evaluate likely impacts of the SEARCH interventions should they be rolled out to a larger community base (thus diminishing the role of external mixing), we assumed a closed cohort with no external mixing and estimated HIV incidence in each arm based on year 3 viral suppression data (Figure 3, Scenario G). In this scenario, the SEARCH intervention and control arms would have reduced 3-year cumulative incidence compared to the counterfactual by 43% (90% UI: 37%, 49%) and 29% (90% UI: 21, 36%), respectively.

## DISCUSSION

The SEARCH study represents an important opportunity to assess the population-level impact of treatment as prevention on HIV incidence. Not only did the trial exceed the UNAIDS 90-90-90 targets overall, but it was also able to achieve high levels of testing, linkage, and viral suppression in populations that have historically been difficult to reach.[10] In this context, HIV incidence declined by 32% over the three years of the study in the intervention arm; however, no difference in cumulative HIV incidence was seen between study arms. Results of this mathematical modeling suggest that this finding may be explained by the substantial increase in viral suppression in the control arm that occurred during the study in the setting of universal baseline HIV testing followed by rapid guideline changes that expanded ART eligibility. Sexual mixing between SEARCH residents with

non-SEARCH community members may also have played a role. The pre-specified trial design had 80% power to detect a 25-40% reduction in incidence, depending on incidence in the control arm, testing coverage among the incidence cohort, and the matched pair coefficient of variation.[22] Using mathematical modeling, we estimated that the study was expected to show between a 4-40% reduction in 3-year cumulative HIV incidence due to the trial interventions, depending on the scenario considered. In particular, a "precision estimate" that incorporated the substantial increases in population-level viral suppression observed in both arms during the trial projected a mean 10% reduction in 3-year cumulative incidence between arms, an effect size that the study was not powered to detect. In short, the absence of a statistically significant difference in incidence between arms seen in the SEARCH study is fully consistent with model-based predictions of a substantial reduction in incidence in both arms due to trial interventions – in particular, universal baseline testing in the context of rapidly expanded ART eligibility.

Importantly, although the trial did not demonstrate a significant reduction in HIV incidence between arms, the true population-level impact of universal test-and-treat is expected to be much greater than what was captured in the study itself. Modeling represents a key opportunity to estimate the effect of SEARCH interventions without the baseline testing campaign – a topic of interest for HIV elimination strategies. Compared to a counterfactual "true control" with no SEARCH baseline testing or interventions, our model estimated that the intervention arm would have reduced 3-year cumulative incidence by 27% to 45%, depending on the degree of external mixing with persons not exposed to the intervention. In a real-world scenario of test-and-treat, external mixing will pose less of an issue as ART coverage among surrounding communities increases. A similar phenomenon of increases in background ART coverage diluting the detectable effect of universal ART occurred in the HPTN 071 trial, which found that providing ART according to community guidelines reduced HIV incidence by 30% compared to standard of care, but universal ART provision did not have a statistically significant effect on incidence.[23] Taken together, the results of the TasP trials indicate that universal test-and-treat, in addition to other combination prevention interventions, can reduce HIV incidence substantially.[8,23-25]

Finally, because the modelers were formally blinded to all incidence results, model-based projections (in particular, the "precision estimate" incorporating data on mobility and post-baseline viral suppression not available at the start of the study) provide a rare opportunity for prospective model validation. The mean relative effect size under the precision estimate (RR 0.90; 90% UI: 0.81, 1.00) was highly consistent with trial results (RR: 0.95, 95% CI 0.77-1.17).[8] Model-based projections of arm-specific cumulative incidence were somewhat higher than those observed in the trial (0.77% and 0.81% for intervention and control, respectively); however, interestingly they were similar to model-based projections of cumulative incidence based on observed post-baseline viral suppression, but assuming minimal external mixing.

There are several model-based limitations of this analysis. First, relative risk of transmission according to viral load is not explicitly modelled; all individuals on ART in the model have a 92% reduced risk of transmission, such that no individual on ART has a 0% probability of transmitting HIV. Second, sexual behavior data were not collected in SEARCH, such that

our modelled sexual network may not represent true patterns of relationship formation in the SEARCH communities. In particular, the sexual network may differ substantially between the three regions represented in the trial. Thirdly, the model does not explicitly model migration between, into, or out of nodes. While mobility may be a key element of HIV acquisition risk, sexual mixing with partners outside the SEARCH community was implicitly modelled by stratifying the population by residency. Finally, we did not examine the potential effects of heterogeneity in suppression in this analysis. Approximately 20% of the HIV-positive population in the intervention arm remained unsuppressed after two years of follow-up,[10] and it will be critical to understand the characteristics and behavior of these individuals in order to ensure that viral suppression interventions reach those at risk of transmitting.[20]

Some have hypothesized that heterogeneity in individual-level risk of HIV transmission prohibits a dose-response relationship between population-level viral suppression and reductions in incidence.[26] However, our modeling in SEARCH closely predicted actual reductions in incidence, which largely did reflect a dose-response relationship. Thus, achieving targets like 90-90-90 or 95-95-95 can, at least in some settings, result in an incidence decline proportional to the decline in population viremia.

In summary, both arms of the SEARCH study achieved high levels of population-level HIV viral suppression, likely due to the presence of baseline testing in both arms and the rapid expansion and uptake of ART eligibility that occurred during the trial. In this context, the modelled effect size was smaller than the trial was powered to detect; the results of the trial are thus consistent with a substantial impact of increased population-level suppression on reduced HIV incidence. Our results support the role of treatment as prevention as a highly effective method for reducing HIV incidence.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BLJ, LBB, MLP, DVH, and AB conceived of the study. BLJ and AB conducted the modeling analyses. BLJ drafted the manuscript. BLJ, LBB, TDC, EDC, DK, MRK, DVH, MLP, and AB contributed to thoughtful interpretation of data and critical revision of the manuscript.

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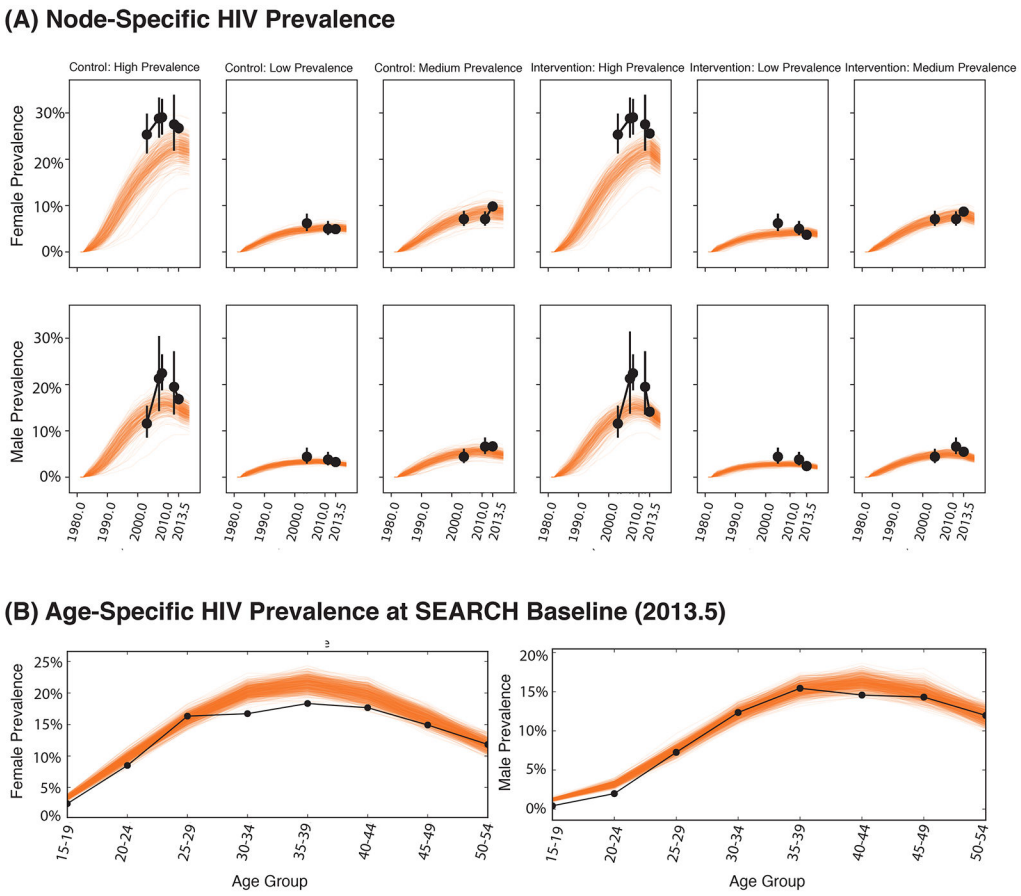


**Figure 1:**

Modeled HIV prevalence among adults (aged 15-49) over time for six nodes (A) and sex- and age-specific HIV prevalence at SEARCH baseline in 2013 (B). Each orange line represents one of 250 selected model trajectories; black dots and bars represent data. In (A), data prior to 2013.5 is taken from regional DHS survey data that corresponds with the respective region of nodes of the SEARCH communities, but does not match the boundaries of the communities directly.

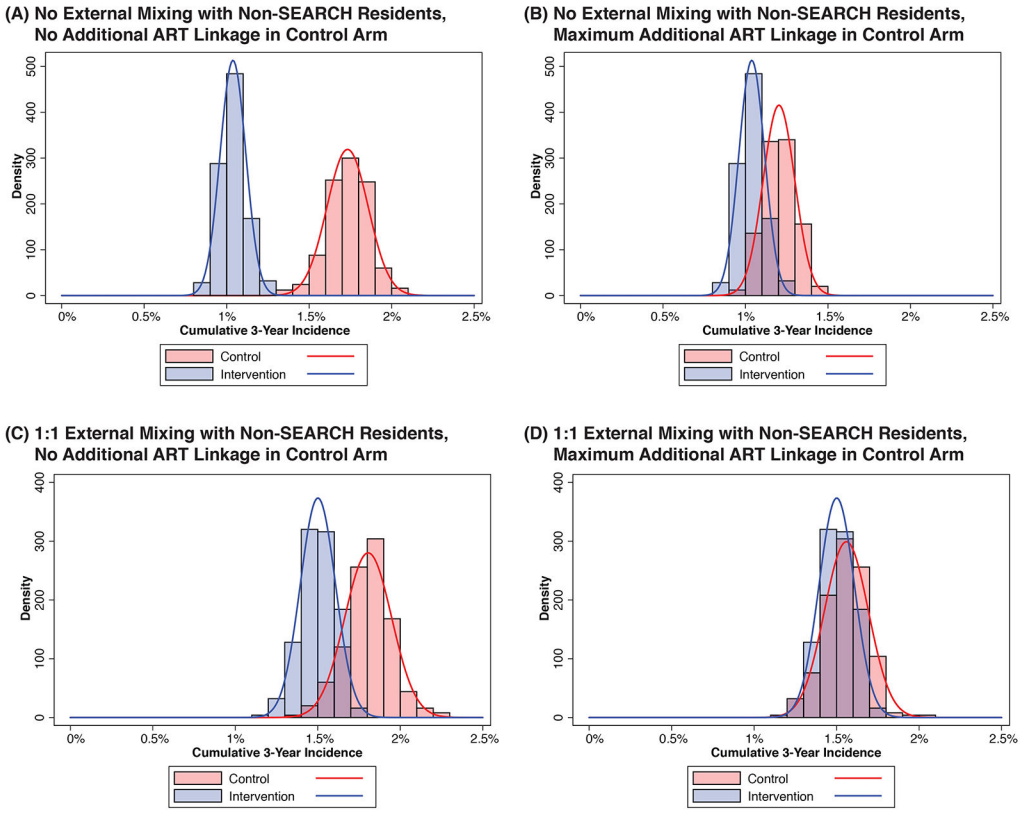


**Figure 2:**

Cumulative 3-year incidence in the control and intervention arms of the SEARCH study, based on different assumptions of mixing between SEARCH and non-SEARCH community members and ART scale-up in the control arm. In 2A, we assumed no external mixing and no additional linkage (i.e., a closed cohort with no active control); in 2B, we assumed no external mixing and maximum ART linkage due to the baseline testing campaign; in 2C, we assumed equivalent mixing between SEARCH residents and non-residents and no additional linkage; in 2D, we assumed equivalent mixing and maximum additional ART linkage.

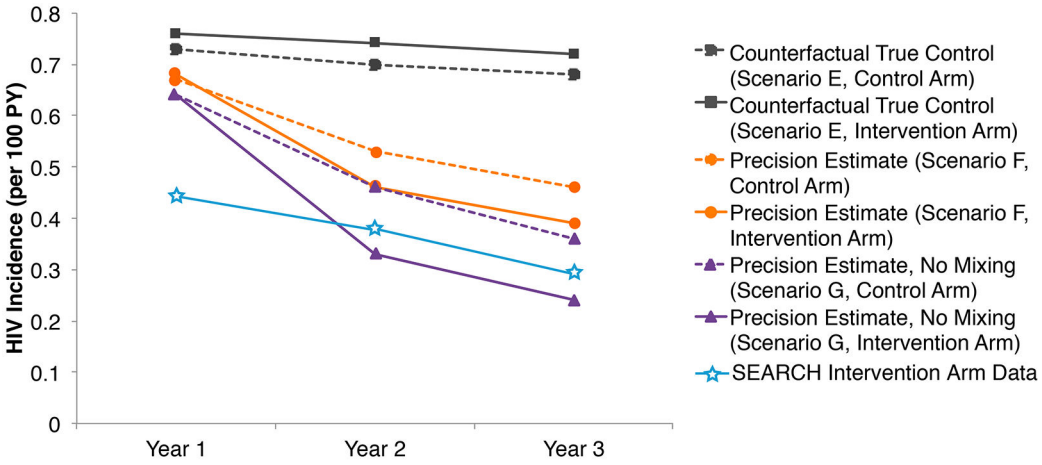


**Figure 3:**

Modeled annual incidence (per 100 person-years) over time in the control (dashed lines) and intervention (solid lines) arms of the SEARCH trial, under three different scenarios: a counterfactual "true control" with no SEARCH baseline testing or interventions in either arm of the trial (gray), year 3 viral suppression in both arms of the trial but no mixing (purple), and "precision estimate" assumptions informed by baseline mobility and year 3 viral suppression in both arms of the trial (orange). Solid lines represent the intervention arm and dashed lines represent the control arm.

**Table 1:**

Definitions of modelled scenarios in Figure 2 and Figure 3.

| Scenario Name | Control Arm Linkage Assumptions | External Mixing Assumptions |
|---|---|---|
| A | "True control": 0% additional linkage from baseline testing, resulting in 69% viral suppression among all baseline HIV+ in SEARCH control communities by Y3 | 0% mixing with non-SEARCH community members |
| B | "Active control": 100% additional linkage from baseline testing, resulting in 76% viral suppression among all baseline HIV+ in SEARCH control communities by Y3 | 0% mixing with non-SEARCH community members |
| C | "True control": 0% additional linkage from baseline testing, resulting in 69% viral suppression among all baseline HIV+ in SEARCH control communities by Y3 | 50% mixing with non-SEARCH community members |
| D | "Active control": 100% additional linkage from baseline testing; results in 76% viral suppression among all baseline HIV+ in SEARCH control communities by Y3 | 50% mixing with non-SEARCH community members |
| E | "True control": no SEARCH baseline testing or interventions in both arms; results in 69% viral suppression among all baseline HIV+ in SEARCH control communities by Y3 | N/A; no individuals receive testing or interventions |
| F ("precision estimate") | Y3 viral suppression from SEARCH: 81% viral suppression in control arm and 89% suppression in intervention arm[†], among all baseline HIV+ in SEARCH control communities | Node-specific 29-41% mixing with non-SEARCH community members[*] |
| G | Y3 viral suppression from SEARCH: 81% suppression in control arm and 89% suppression in intervention arm[†], among all HIV+ | 0% mixing with non-SEARCH community members |

[†]Viral suppression numbers estimated from SEARCH data on baseline HIV+ stable residents (i.e., those residing in the community for ≥ 6 months out of the year) only, not allowing for in-migration.

[*]Mixing estimated from node-specific baseline mobility.