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Community-Wide Universal HIV Test and Treat Intervention Reduces Tuberculosis Transmission in Rural Uganda: A Cluster-Randomized Trial

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Background. Human immunodeficiency virus (HIV) treatment reduces tuberculosis (TB) disease and mortality; however, the population-level impact of universal HIV-test-and-treat interventions on TB infection and transmission remain unclear.

Methods. In a sub-study nested in the SEARCH trial, a community cluster-randomized trial (NCT01864603), we assessed whether a universal HIV-test-and-treat intervention reduced population-level incident TB infection in rural Uganda. Intervention communities received annual, population-level HIV testing and patient-centered linkage. Control communities received population-level HIV testing at baseline and endline. We compared estimated incident TB infection by arms, defined by tuberculin skin test conversion in a cohort of persons aged 5 and older, adjusting for participation and predictors of infection, and accounting for clustering.

Results. Of the 32 trial communities, 9 were included, comprising 90 801 participants (43 127 intervention and 47 674 control). One-year cumulative incidence of TB infection was 16% in the intervention and 22% in the control; SEARCH reduced the population-level risk of incident TB infection by 27% (adjusted risk ratio = 0.73; 95% confidence interval [CI]: .57–.92, $P = .005$). In pre-specified analyses, the effect was largest among children aged 5–11 years and males.

Conclusions. A universal HIV-test-and-treat intervention reduced incident TB infection, a marker of population-level TB transmission. Investments in community-level HIV interventions have broader population-level benefits, including TB reductions.

Keywords. tuberculosis; HIV; tuberculosis transmission.

Global human immunodeficiency virus (HIV) and tuberculosis (TB) are linked epidemics [1, 2]. HIV infections fuel TB disease, both by reactivation of latent TB infection and increasing susceptibility to progression to active TB disease once exposed. While individual- and population-level benefits of antiretroviral therapy (ART) on reducing TB disease among people with HIV (PWH) are well established [3–5], the impact on community-wide TB transmission (new TB infections) remains unclear. Interrupting TB transmission is critical to ending the TB epidemic, especially as ongoing TB transmission perpetually produces new TB disease cases and latent infections.

The SEARCH intervention (NCT01864603), a universal HIV-test-and-treat strategy, consisted of annual population-based HIV and multi-disease testing with a patient-centered care strategy [5]. The intervention reduced the population-level incidence of TB disease by 59% (relative rate = 0.41; 95% confidence interval [CI]: .18–.86) among PWH in rural Uganda and Kenya [5]. Additionally, the intervention rapidly increased population-level HIV viral suppression [5], improved community health outcomes, such as decreased mortality among PWH [5, 6], and improved markers of financial well-being [7]. The impact of this intervention and other "universal HIV-test-and-treat" interventions on TB transmission has not been previously assessed.

Community-wide interventions aimed at increasing HIV virologic suppression may have a significant effect on TB transmission by decreasing susceptibility of PWH to developing TB disease and thereby decreasing the incidence of infectious TB cases leading to fewer new TB infections on a population-

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level. Thus, in a sub-study of a cluster-randomized controlled trial, we sought to assess the impact of the SEARCH intervention—a universal HIV test-and-treat strategy with patient-centered streamlined care for HIV and chronic diseases—on population-level TB transmission, using incident TB infection in children and adults as measures of ongoing TB transmission.

METHODS

Study Design, Setting, and Participants

This was a sub-study of the cluster-randomized SEARCH trial (NCT01864603). The SEARCH trial's study design, randomization procedures, outcomes, and protocol have been described previously [5]. Briefly, it was a 32-community-randomized control trial in rural Uganda and Kenya from 2013 to 2017 that sought to evaluate the effect of universal HIV testing with immediate ART regardless of CD4 count, delivered via a multi-disease testing approach with streamlined patient-centered HIV care delivery [5, 8, 9] (Supplementary Figure 1). Population-based HIV testing and multi-disease community health campaigns (CHCs) were repeated annually in intervention communities, and at baseline and endline for control communities. CHCs included HIV testing and screening for diabetes, hypertension and active TB in Eastern Uganda only. For TB screening at the CHCs, all residents 15 years and older reporting a cough > 2 weeks provided 2 spot sputum samples for acid fast bacilli (AFB) microscopy [10]. Intervention communities had patient-centered streamlined care that focused on reducing structural barriers to care and improving relationships between patients and providers [8]. Control communities received country guided HIV care with ART eligibility guided by country guidelines. At the time of the study, isoniazid preventive therapy (IPT) initiation was low, consistent with national data showing TPT coverage among PWH of 0.6% in 2016% and 1.2% in 2017 [11].

Incident TB infection was measured in a nested sub-study in 9 of the 10 communities in eastern Uganda. Communities were conveniently selected to ensure robust inference for the region and to leverage the ongoing socioeconomic survey [7], which covered about 10% of residents in each community, enriched for PWH. The sub-study randomly sampled 100 households with at least 1 adult (age ≥ 15 years) with HIV and 100 households without HIV. These households were visited annually, and all household members aged 5 or older were eligible for screening for TB infection. Children under 5 years were excluded to minimize false positives due to bacillus Calmette-Guérin (BCG) vaccination [12–14]. Research assistants visited each of the participating households up to 3 times for tuberculin skin testing (TST) placement and to administer a TB-specific questionnaire. Baseline TSTs were placed from 2015–2016. Follow-up TSTs were placed 1 year later (2016–2017) in all persons who had negative TSTs at baseline. TSTs were performed per standard protocol using Tubersol tuberculin [15].

Measures

The primary outcome for this sub-study was incident TB infection, defined as a conversion from a negative TST at baseline to a positive TST at one-year follow-up. A positive TST was defined as an induration of ≥10 mm for people without HIV and ≥5 mm for PWH. Through the parent SEARCH study, we conducted a rapid census and measured demographic factors, including age, gender, occupation, mobility, and alcohol use. We defined occupations as high risk for TB if they involved significant contact with others outside of the home, such as shopkeeper, while low-risk occupations included predominantly outdoor occupations like farmer. Highly mobile participants were defined as those living ≥1 months outside of the parish (an administrative subunit of a community) in the past year. HIV status was defined as testing positive at baseline in the SEARCH trial, where adult HIV testing coverage was over 90% [16]. Household wealth was assessed with measurement of household assets (eg, radio, clock) and livestock, categorized using a principal component analysis, and summarized into wealth index quintiles [17, 18]. In the nested TB sub-study, we measured history of self-reported active TB disease, TB contact within the last year, and receipt of BCG vaccine, defined as the presence of a scar on the or having documentation of vaccine receipt.

Statistical Analysis

This was a sub-study of the SEARCH trial, where 32 communities were randomized to the intervention or control conditions, within matched pairs and during community participatory events, as previously described [5]. Sample size and power calculations were conducted for the parent trial's primary outcome, HIV incidence, as previously described [5]. Communities or participants were not masked to randomization group, but study statisticians were masked until trial completion. All analyses were conducted according to a prespecified analysis plan (Supplementary Statistical analysis).

The primary objective was to evaluate the effect of the SEARCH intervention on 1-year incident TB infection among children and adults aged 5 years and older in the 9 communities in Uganda participating in the TB sub-study. To do so, we compared incident TB infection by arm using a 2-stage targeted maximum likelihood estimation (TMLE), accounting for clustering, the sub-study sampling scheme, and missingness on baseline and follow-up TSTs [19, 20]. Two-stage TMLE is a doubly robust method, combining estimates of the expected outcome with the propensity score and was previously applied in the primary analysis of the parent SEARCH trial [5]. In this application, we first estimated the incidence of TB infection in each parish, adjusting for participant-level factors influencing TB risk, sampling, and outcome measurement at both baseline and follow-up: household HIV status, age, and mobility. Second, we compared these incidence estimates between

randomized arms using a cluster-level TMLE, adjusting for HIV prevalence and alcohol use prevalence to increase precision and account for within-community dependence. Few clusters prohibited further adjustment during effect estimation in the second stage; additional details on the statistical methods are available in our companion paper [20].

Our 2-stage approach provides estimates of the incidence of TB infection, which are generalizable to all community members, even those not included in the sub-study sample or those included in the sample but missing baseline or follow-up TSTs. Our approach also provides population-level estimates of the SEARCH effect on the incidence of TB infection in rural Eastern Uganda. We tested the null hypothesis of no effect of the SEARCH intervention with a one-sided test at the 5% significance level and provided 95% confidence intervals. We repeated these analyses within subgroups defined by gender and age. Specifically, given our prior work demonstrating changes in TB risk and prevalence between childhood and adolescence [15], we considered 2 age groups: 5–11 years and ≥12 years.

Ethical Considerations

Participants provided written informed consent or assent in their local language for participation; informed consent for children was provided by a parent or legal guardian. Community-level consent was obtained prior to randomization [5]. The Makerere University School of Medicine Research and Ethics Committee (Uganda) and Uganda National Council for Science and Technology (Uganda) and the University of California, San Francisco Committee on Human Research (USA) approved the consent and study procedures.

RESULTS

Of the 32 communities in the SEARCH trial, 9 were included in the sub-study, with 4 communities in the intervention arm and 5 communities in the control. The enumerated population consisted of 90 801 persons, with 43 127 in the intervention and 47 674 in the control (Figure 1, consort diagram). Descriptive characteristics of the target population are found in Table 1 and were balanced by arm with the exception of alcohol use (among those aged ≥12 years): 18% in the intervention and 11% in the control. Overall, the median age was 17 (25%–75% quartiles: 10–32), 54% female, 30% were between the ages of 5 and 11 years, and 21% were highly mobile. Among those aged ≥12 years, 61% had less than a primary school education level, 3.3% were PWH, and 33% had a high TB risk occupation.

Overall, 8420/90 801 (9%) persons were sampled for participation in the TB infection sub-study, 3761/43 127 (9%) persons in the intervention arm and 4659/47 674 (10%) in the control arm (Supplementary Table 1). By design, the sub-study was enriched for households with ≥1 adult with HIV. As a result, HIV prevalence (among ≥12 years) was 18% among those

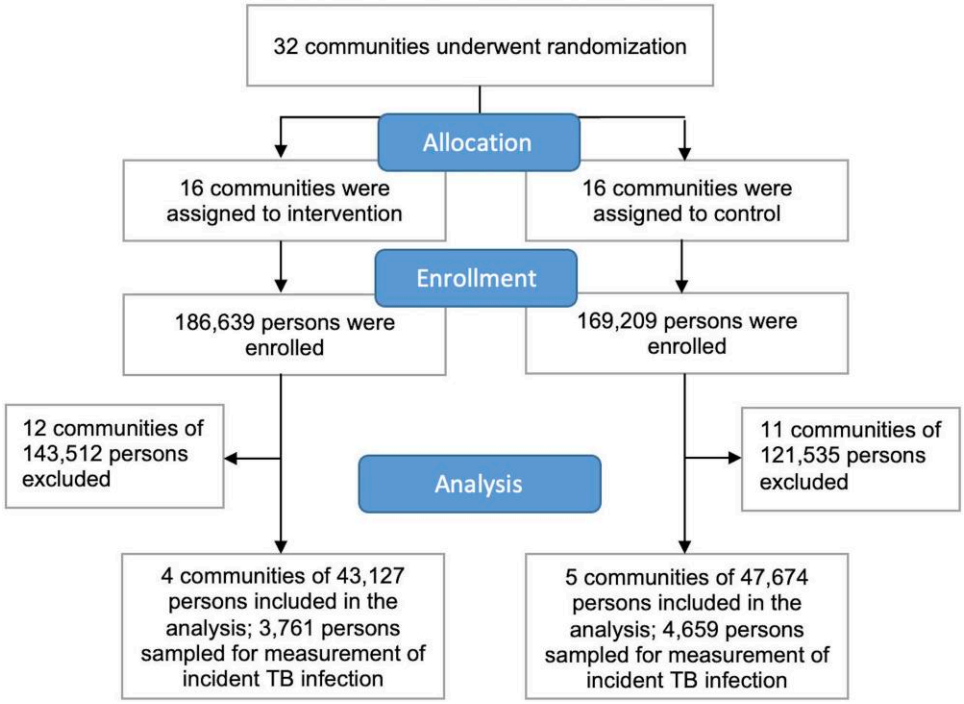

Figure 1. Consort diagram. Abbreviation: TB, tuberculosis.

Table 1. Baseline Demographics of Residents of the Sub-study Communities, Stratified by Trial Arm

	Intervention	Control	Total
N	43 127	47 674	90 801
Median age [Q1, Q3]	18 [10, 32]	17 [10, 31]	17 [10, 32]
5–11 y	12 569 (29.1%)	14 546 (30.5%)	27 115 (29.9%)
≥12 years	30 558 (70.9%)	33 128 (69.5%)	63 686 (70.1%)
Gender			
Men	19 756 (45.8%)	22 405 (47%)	42 161 (46.4%)
Women	23 368 (54.2%)	25 269 (53%)	48 637 (53.6%)
High mobility[a]	9770 (22.7%)	9264 (19.4%)	19 034 (21%)
Household wealth quintile			
1st	6603 (15.8%)	6877 (15%)	13 480 (15.4%)
2nd	8145 (19.5%)	8644 (18.9%)	16 789 (19.2%)
3rd	9322 (22.3%)	9750 (21.3%)	19 072 (21.8%)
4th	9120 (21.8%)	10 579 (23.1%)	19 699 (22.5%)
5th	8579 (20.5%)	9905 (21.6%)	18 484 (21.1%)
Education completed[b]	…	…	…
Below primary	14 660 (61.2%)	15 394 (60%)	30 054 (60.6%)
Primary	2995 (12.5%)	3403 (13.3%)	6398 (12.9%)
Any secondary	6287 (26.3%)	6855 (26.7%)	13 142 (26.5%)
With HIV[b]	804 (3.3%)	869 (3.2%)	1673 (3.3%)
High TB risk occupation[b,c]	8197 (33.4%)	8772 (32.2%)	16 969 (32.8%)
Alcohol use[b]	4460 (17.6%)	3193 (11.3%)	7653 (14.3%)

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

[a]High mobility participants were defined as living one or more months outside of the parish in the past year.

[b]Among participants aged ≥12 years.

[c]High-risk occupations for TB included occupations with significant contact with others outside of the home, such as shopkeeper or factory worker, while low-risk occupations included things like farmer and disabled or unemployed.

sampled for the sub-study, substantially larger than the prevalence in the target population (3.3%). Of the 8420 persons sampled for the incident TB sub-study, 4884 (58%) had TSTs placed and read at baseline; the remaining 3536 declined participation or were not home for TST placement. TST coverage was similar by arm: 60% (2243/3761) in intervention and 57% (2641/4659) in control but varied by age and mobility at baseline (Supplementary Table 2). Overall, among 4884 tested at baseline, 4532 (93%) had a record of BCG vaccination or a scar, 170 (3.9%) reported TB contact, and 40 (0.8%) reported a history of TB disease. A total of 3831 participants were TST-negative at baseline with 1724 in the intervention and 2107 in the control. After 1 year, 63% (2425/3831) had a TST placed and read. Follow-up coverage was similar by arm: 62% (1065/1724) intervention and 65% (1360/2107) control but again varied by age group and mobility (Supplementary Table 2).

Accounting for sampling and unknown TB status on sampled participants, the estimated prevalence of latent TB at baseline was 24% (95% CI: 22%–25%) overall and similar by arm: 24% (95% CI: 22%–27%) in the intervention versus 23% (95% CI: 21%–25%) in the control. Baseline prevalence varied by age and was 8% (95% CI: 6%–10%) among children aged 5–11 years versus 31% (95% CI: 29%–32%) among people aged ≥12 years. The prevalence of latent TB at baseline was also higher among males (27% [95% CI: 24%–29%]) than females (22% [95% CI: 20%–25%]).

Accounting for sampling and missingness on baseline and follow-up TB status, the estimated 1-year cumulative incidence of TB infection was 16% (95% CI: 13%–20%) in the intervention arm and 22% (95% CI: 17%–27%) control. Thus, the intervention reduced the population-level risk of incident TB infection by 27% (adjusted risk ratio [aRR] of 0.73; 95% CI: .57–.92, $P = .005$). Pre-specified subgroup analyses showed intervention effects on TB incidence in children aged 5–11 years (aRR 0.67; 95% CI: .45–1.01, $P = .027$) and in people age ≥12 (aRR 0.80; 95% CI: .64–1.00, $P = .026$; Figure 2). Pre-specified subgroup analyses by gender showed a 37% reduction in the risk of incident TB infection in males (aRR 0.63, 95% CI: .41–.97, $P = .020$), but no reduction was detected among females (aRR 0.96; 95% CI: .65–1.42, $P = .408$, Figure 2).

DISCUSSION

The multi-component SEARCH intervention, a universal HIV and multi-disease test-and-treat strategy with patient-centered linkage and care, reduced one-year cumulative incidence of TB infection by 27% on a population-level. Upstream interventions that can both prevent infection and reduce the intensity of community-wide transmission are critical to ending the TB epidemic. Prior interventions showing an impact on TB transmission were predominantly multi-component TB active case finding interventions [21–25]; however, this study was, to our knowledge, the first to show a population-level impact of a multi-component HIV-specific intervention on incident TB infection, a proxy for community transmission, and an impact on children. Ending the TB epidemic in high HIV and TB burden settings will require multi-factorial interventions that not only scale-up TB specific interventions, such as treating latent TB infection and active TB case finding, but also those addressing the contributing HIV syndemic.

We hypothesize that the SEARCH intervention decreased community-wide TB transmission through multiple mechanisms: (1) decreasing community-wide prevalence of TB disease, (2) decreasing overall infectiousness of people with TB, and (3) impacting social determinants of health that increase the risk of acquiring TB (Figure 3). First, a rise in population-level viral suppression likely decreased susceptibility to developing active TB disease, either through reactivation among those with latent TB infection or primary progression [1, 26]. This hypothesis is supported by biologic plausibility and our prior finding that the SEARCH intervention decreased the cumulative incidence of HIV-associated TB disease over 3 years.[5] Second, high levels of care engagement for HIV and chronic diseases in the intervention arm may have decreased the duration of infectiousness of TB cases through earlier TB diagnosis

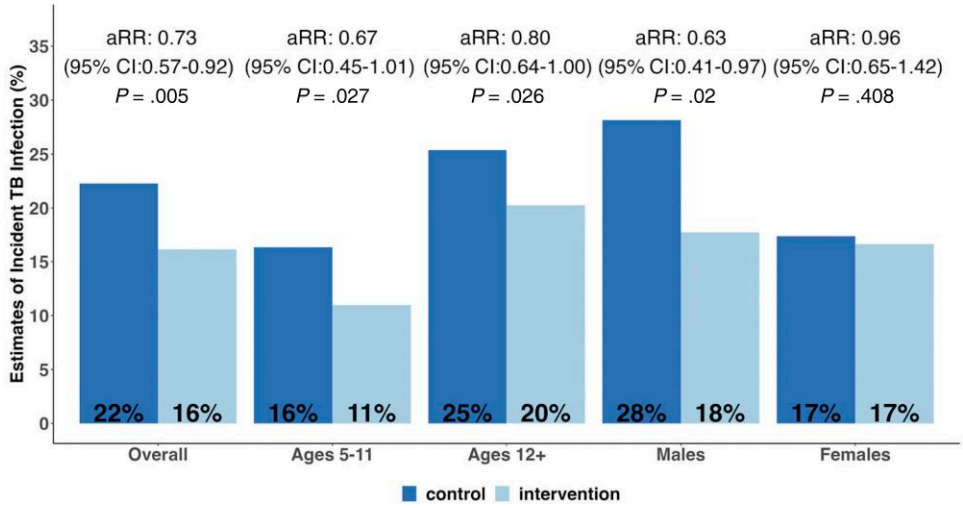

Figure 2. Effect of the SEARCH HIV test and treat intervention on incident TB infection, overall and stratified by pre-specified subgroups—age group and gender. Incident TB infection was defined by TST conversion from negative at baseline (area of induration <10 mm or <5 mm if person with HIV) to positive (area of induration ≥10 mm or ≥5 mm if person with HIV). Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; HIV, human immunodeficiency virus; TB, tuberculosis; TST, tuberculin skin test.

and treatment initiation [2, 27]. Active case finding (ACF) with smear microscopy was performed more frequently in intervention arms, which may have contributed to the intervention effect, by lowering the duration of infectiousness of people with active TB. However, only small numbers of people with TB disease were identified through ACF. For example, in the baseline ACF identified 9 smear-positive cases overall (0.3% of CHC participants ≥15 years) [10]. Finally, the SEARCH intervention's positive impact on economic indicators among PWH [7] may have also decreased sociodemographic risk factors that increase TB susceptibility such as malnutrition and environmental risk factors: household crowding or social mixing patterns [28–30]. TB preventive therapy was not routinely administered in Uganda at the time of this study; its addition to the intervention would likely have reduced community-wide TB transmission even further given its effectiveness in reducing TB disease and transmission, especially in concert with ART [3].

The 1-year estiamted cumulative incidence of TB infection was high in both arms: 22% in control and 16% in intervention, and higher than expected based on the baseline prevalence of TB infection [15]. Nonetheless, this finding is consistent with other longitudinal studies in high-TB burden settings that found that cross-sectional studies of TB infection markedly underestimate incidence due to a high rate of TST reversion [31, 32]. For example, in a large study in South African adolescents, the incidence of TB infection measured by TST was 13%, and the annual risk of infection was 8 times higher when estimated longitudinally compared to cross-sectionally [31]. Our data extend the findings from South Africa and highlight the high rate of TB transmission in a rural setting in East Africa.

Subgroup analyses highlight the impact of the community-based HIV interventions on new TB infections among school-aged children. Infection in children is a sentinel of TB transmission, and to our knowledge this study is one of the first to show a population-level impact on incident TB infection in children. The ZAMSTAR trial, a household-based active TB and HIV care intervention in South Africa and Zambia, suggested a reduction of TB transmission as measured by incident TB infection in a TST negative cohort in children, although the effect did not meet statistical significance [25]. Together, findings from the SEARCH and ZAMSTAR trials suggest that community-based interventions focused on adults in the community can reduce TB infection in children.

The SEARCH intervention resulted in a 37% reduction in incident TB infection among men and boys. Sex-specific disparities in TB are well established [33–35], with men comprising a higher proportion of TB cases and a modeling study from South Africa and Zambia suggests that over 57%–66% of cases are attributable to contact with adult men with TB [36]. Much of this disparity in cases and transmission is attributed to sex-assortative mixing within social-spatial networks [35, 37, 38], and we previously showed that people with more men in their network, regardless of individual-level risk factors, had a higher risk of TB infection [39]. The SEARCH intervention may have shown an effect more quickly in men because of higher transmission in their social spatial networks.

The results of this study should be interpreted considering its strengths and limitations. There is no gold standard for measurement of TB infection, and TSTs can yield false positives due to BCG vaccination—with higher rates of false positives among those under the age of 7 and false negatives with

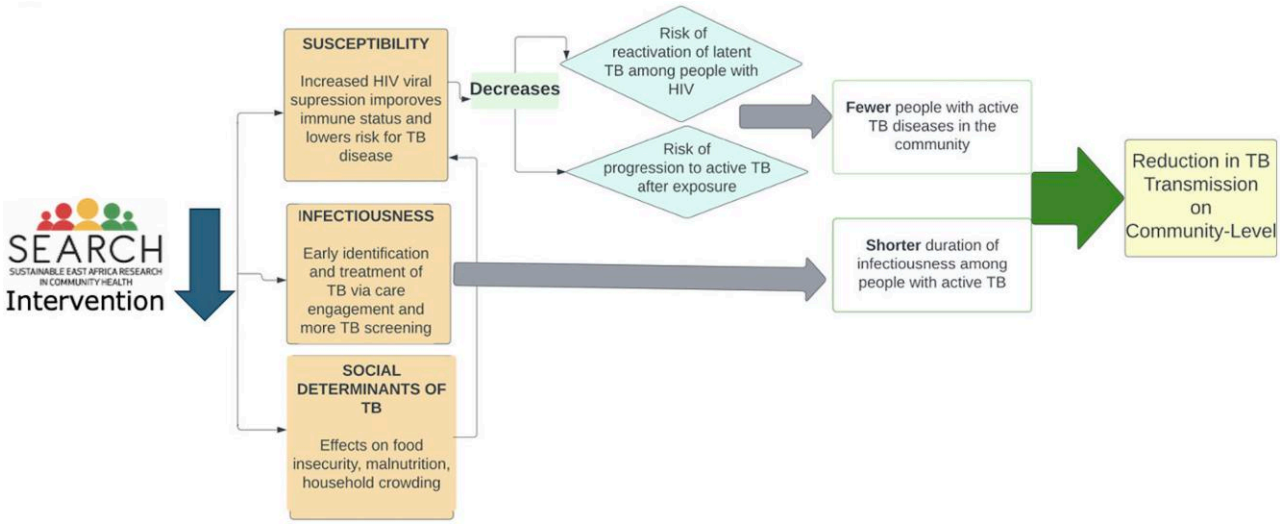

Figure 3. Schema of potential mechanisms in which the SEARCH intervention reduced TB transmission. Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

immunosuppression, HIV [12, 13, 40]. BCG vaccination was high and well balanced between intervention and control, and thus, we expect non-differential misclassification of the outcome due to false positives from BCG between arms and boosting. However, differential rates of virologic suppression may have impacted the results. Specifically, lower rates of virologic suppression [5] in the control arm may have resulted in more false negative TSTs at follow-up, biasing the intervention effects towards the null. Another potential limitation includes bias due to missing data; specifically, there were multiple opportunities for missingness with TST-based measurement of incident TB infection. However, we expect the impact of this missingness to be minimal, given our statistical approach to adjust for differences between participants with a measured versus missing TST at both baseline and follow-up [19, 20]. For these reasons, we purposefully avoided presentation of unadjusted results, which would be biased. Finally, due to logistical and financial constraints, only 9 communities were included the sub-study. With 9 communities, there was a potential for imbalance on outcome predictors between arms. Indeed, the prevalence of alcohol use was higher in the intervention (18%) than control (11%). However, because alcohol use was included in our adjustment set, we do not expect this to bias our results. That said, we cannot rule out the potential for imbalance on unmeasured factors, such as smoking tobacco and indoor air pollution. Strengths of this study include randomized trial design, population-based testing (covering 90% of the adults), the inclusion of children, and rigorous statistical methods.

In an expanded context of a community-wide HIV intervention designed to address critical elements of the HIV/TB co-epidemic, our data demonstrate a TB incidence reduction through a multicomponent, community-based universal HIV-test-and-treat intervention. These data add to the significant and broad community-health benefits of population level approaches to the testing and universal treatment of HIV.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Prior presentations. These data were presented in part as an oral presentation at the AIDS 2022 conference in Montreal, Canada, July 2022 OAB0403.

Potential conflicts of interest. G. C. reports participation on a data safety monitoring board or advisory board as a member of a data monitoring committee for an NIH-funded clinical trial (TB Screening Improves Preventive Therapy Uptake [TB SCRIPT] trial). E. D. C. reports consulting fees from the Infectious Diseases Research Collaboration, Kampala, Uganda (paid to the author for Integrated HIV and Hypertension Study consulting). D. V. H. reports nonfinancial support from Gilead (drug donation for an NIH study) and Abbott (diagnostic test donation). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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