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Study Summary

This study evaluated HIV incidence among persons initiating pre-exposure prophylaxis (PrEP) when universal access to PrEP with a flexible service delivery model was offered as part of the population-level Sustainable East Africa Research in Community Health (SEARCH) study, compared to historical controls.

Study Setting

- Sixteen of the 32 communities in rural Kenya and Uganda that were part of the SEARCH study.

Methods

- The SEARCH study is a cluster-randomized controlled trial that began in 2013 and compares the impact of "test and treat" with universal antiretroviral therapy (ART) using a multi-disease, patient-centered care model to standard care on HIV incidence and other community health outcomes.[1]
- From 2016 to 2017, the study implemented a population-level PrEP intervention before national PrEP rollout in Kenya and Uganda. The intervention included:
    - Community sensitization and education on PrEP.
    - Universal access to PrEP during population-level HIV and multi-disease testing, offered at health fairs at multiple locations across each community over two weeks, followed by home-based testing for non-attendees.
    - Enhanced individual counseling on PrEP for people considered to have an elevated risk of HIV acquisition, including: 1) people in serodifferent partnerships; 2) those classified as being at risk based on an empirical HIV risk prediction algorithm developed using machine learning; and 3) individuals who self-identified as being at risk.
    - Rapid or same-day PrEP initiation at local government clinics, with study-provided transport, as well as on-site PrEP initiation at SEARCH community-wide health fairs in 14/16 communities, and ongoing provision of PrEP at clinics in all study communities.
    - On-site PrEP initiation during HIV testing events for key and priority populations, including serodifferent partners, young women, and persons working in the fishing or transportation industries or in bars, between 2017 and 2018.

    - A flexible refill system with options for follow-up visits at clinics or community locations of the participants' choice (e.g., homes, near schools, trading centers, or beaches).
- PrEP eligibility criteria included a negative HIV test within the preceding four weeks, no known hepatitis B infection, and no acute HIV symptoms. Baseline creatinine testing was performed, but PrEP was provided before the receipt of results.
- Follow-up visits were scheduled at week 4, week 12, and every 12 weeks thereafter for up to 144 weeks, after which participants were referred to local clinics for ongoing care.
- Follow-up visits included evaluation of self-assessed HIV risk, self-reported PrEP adherence using 3-day recall, HIV testing, and PrEP refills. Participants who stopped PrEP were offered HIV testing and the opportunity to restart PrEP at each visit.
- Participants who tested positive for HIV, using the national testing algorithm, were offered same-day ART and received confirmatory testing with HIV RNA or western blot if HIV RNA was not detected. Plasma samples were also collected for assessment of resistance to antiretroviral (ARV) drugs.
- Among participants who self-reported taking PrEP ≤30 days prior to seroconversion, small hair samples were collected for analysis of tenofovir concentrations to estimate the number of PrEP doses taken per week.
- Among participants with incident HIV infection, viral suppression ≤12 months after ART initiation was assessed (defined as HIV RNA <1,000 copies/ml).
- The HIV incidence rate was calculated among PrEP initiators who had repeat HIV testing after PrEP initiation, and compared to expected HIV incidence without PrEP.
- The expected incidence rate was calculated based HIV incidence among propensity score-matched recent controls. The controls were from the eight study communities in which population-level HIV testing was performed one year before PrEP was available (2015 to 2016) and repeated one year later (2016 to 2017) at the start of the PrEP intervention.
- Individuals who tested HIV negative in 2015 or 2016 and had a repeat HIV test one year later were eligible to contribute to the analysis. Controls were selected based on 1-to-1 matching on an estimated propensity score, defined as the conditional probability of PrEP initiation given HIV risk predictors including age, sex, occupation, education, mobility, alcohol use, and serodifferent partnership.

<u>Study Population and Follow-up</u>

- From June 2016 to April 2019, 76,132 individuals ≥15 years old received HIV testing in the 16 study communities, of whom 74,541 tested negative for HIV.
- Of those testing negative, 15,632 (21%) were assessed to be at elevated risk of HIV acquisition, and 5,447 (35%) initiated PrEP.

- Among the PrEP initiators, 49% were women, 29% were age 15 to 24 years, 16% were age ≥45 years, and 19% were in serodifferent partnerships.

PrEP Uptake

- Among 5,398 PrEP initiators eligible for a follow-up visit, 4,271 (79%) attended ≥1 follow-up visit, 3,578 (66%) received ≥1 refill, and 3,282 (61%) self-reported adherence to PrEP (defined as taking at least one of the last three doses) at ≥1 visit.
- Declines in PrEP program engagement (65% at week 4 vs. 54% at week 60), refills (52% vs. 33%) and self-reported adherence (42% vs. 27%) among eligible participants were seen over time.
- Among participants reporting current HIV risk at follow-up visits, refills and self-reported adherence were higher, with 94% receiving refills and 75% reporting adherence at week 60.
- Overall, 83% of PrEP initiators stopped PrEP at least once and 45% of those later restarted PrEP.
- Throughout the study, women were more likely than men to ever engage in visits (82% vs. 75%), receive refills (69% vs. 62%), or report adherence (65% vs. 56%).

HIV Incidence

- Among 4,260 (78%) PrEP initiators who had ≥1 subsequent HIV test, there were 25 incident HIV infections over 7,150 person-years of follow-up.
- The HIV incidence rate was 0.35 per 100 person-years (95% confidence interval [CI] 0.22 - 0.49) overall, 0.46 per 100 person-years (95% CI 0.24 - 0.68) among women, and 0.23 per 100 person-years (95% CI 0.09 - 0.41) among men.
- Among matched recent controls, there were 17 incident HIV infections over 1,848 person-years of follow-up, amounting to an HIV incidence rate of 0.92 per 100 person-years (95% CI 0.49 - 1.41).
- Among PrEP initiators in the same eight communities as the controls, the HIV incidence rate was 0.32 per 100 person-years (95% CI 0.15 - 0.53), corresponding to 74% lower HIV incidence among PrEP initiators compared to matched recent controls (adjusted incidence rate ratio [aIRR] 0.26, 95% CI 0.09 - 0.75; p=0.013).
- Among women, HIV incidence among matched controls was 1.52 per 100 person-years (95% CI 0.70 - 2.36) compared to 0.40 per 100 person-years (95% CI 0.12 - 0.73) observed among PrEP initiators, corresponding to 76% lower HIV incidence among PrEP initiators (aIRR 0.24, 95% CI 0.07 - 0.79; p=0.019).
- Among men, HIV incidence among matched controls was 0.40 per 100 person-years (95% CI 0.10 - 0.90) compared to 0.24 per 100 person-years (95% CI 0.06 - 0.49) observed among PrEP initiators, corresponding to 40% lower HIV incidence among PrEP initiators that was not statistically significant (aIRR 0.60, 95% CI 0.12 - 3.05; p=0.54).

Seroconverter Characteristics and Outcomes

- Among the 25 individuals with incident HIV infection following PrEP initiation, 17 (68%) were women, and the median age was 27 years (range 20 to 62) among women and 35 years (range 22 to 49) among men.
- Of these, 18/25 (72%) reported not taking PrEP for >30 days before the seroconversion visit.
- Of the seven participants with incident HIV infection who reported taking at least one dose of PrEP in the prior 30 days, four reported intermittent PrEP adherence in the prior three months.
- Three participants seroconverted at the week 4 visit and therefore were possibly acutely infected at study enrolment.
- Among the 25 participants with incident HIV infection, 24 (96%) started ART, 19 of whom had viral load results available and of these 18 (95%) had HIV RNA <1,000 c/ml. One participant was found to have 2-class ARV drug resistance despite high PrEP adherence (tenofovir levels in hair consistent with 7 doses/week) and did not achieve viral suppression initially.
- Overall, two of the 10 participants who underwent genotyping had evidence of drug resistance mutations, one with mutations that were likely transmitted and not related to PrEP use, and the other with mutations which may have been transmitted or acquired on PrEP.

Critical Analysis

This component of the SEARCH study found that expanded access to PrEP after community-wide HIV testing, with a flexible service delivery model and inclusive eligibility criteria, was associated with a lower HIV incidence among PrEP initiators compared to matched historical controls. This effect was more pronounced among women, who had higher HIV incidence rates compared to men in the study.

The following points should be considered when interpreting the study findings:

- In this study, participants were eligible for PrEP initiation if they had a negative HIV test within the last 4 weeks, which could increase the probability of undetected acute HIV infection at initiation compared to more standard, same-day HIV testing before initiation. However, only three participants seroconverted at the week 4 visits, and sensitivity analyses excluding these participants showed similar results.
- A limitation of this study is the lack of a contemporaneous control group, which raises the possibility that secular trends could have contributed to the reduced HIV incidence observed among PrEP initiators. However, the authors note that even after accounting for a reduction in HIV incidence consistent with trends from the prior three years in the study communities, PrEP initiators would have had a 62% lower HIV incidence compared to matched contemporaneous controls.

- Only one in three participants who tested HIV negative and who were estimated to be at elevated risk of HIV acquisition accepted PrEP. Uptake was particularly low among those aged 15-24 and mobile individuals,[2] suggesting more strategies may be required to improve initial acceptance and uptake of PrEP, especially in these groups.
- Many participants stopped and restarted PrEP, suggesting that they recognized periods of risk. However, the majority of the seroconversions occurred after participants had stopped PrEP for >30 days, suggesting that participants may not always judge their HIV risk accurately.
- Despite offering a flexible service delivery model, retention in PrEP services declined over time, with a third of participants not receiving a PrEP refill. This suggests that a variety of prevention options and approaches may be required to meet the prevention needs of more individuals.

Implications

Expanded population-level access to PrEP through the SEARCH study, with a flexible service delivery model, was associated with lower HIV incidence among PrEP initiators in rural Kenya and Uganda compared to historical controls. These findings demonstrate that universal access to PrEP can play a significant role in reducing HIV incidence, even in high-prevalence epidemic settings with universal 'test and treat' programs. As country programs scale-up PrEP services, the flexible, inclusive approach to PrEP provision that was used in this study could serve as a model for service delivery.

References

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