High Rates of Pre-exposure Prophylaxis Eligibility and Associated HIV Incidence in a Population With a Generalized HIV Epidemic in Rakai, Uganda

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Background: The utility of using pre-exposure prophylaxis (PrEP) eligibility assessments to identify eligibility in general populations has not been well studied in sub-Saharan Africa. We used the Rakai Community Cohort Study to conduct a cross-sectional analysis to estimate PrEP eligibility and a cohort analysis to estimate HIV incidence associated with PrEP eligibility.

Methods: Based on Uganda’s national PrEP eligibility tool, we defined eligibility as reporting at least one of the following HIV risks in the past 12 months: sexual intercourse with more than one partner of unknown HIV status; nonmarital sex act without a condom; sex engagement in exchange for money, goods, or services; or experiencing genital ulcers. We used log-binomial and modified Poisson models to estimate prevalence ratios for PrEP eligibility and HIV incidence, respectively.

Findings: We identified 12,764 participants among whom to estimate PrEP eligibility prevalence and 11,363 participants with 17,381 follow-up visits and 30,721 person-years (pys) of observation to estimate HIV incidence. Overall, 29% met at least one of the eligibility criteria. HIV incidence was significantly higher in PrEP-eligible versus non-PrEP-eligible participants (0.91/100 pys versus 0.50/100 pys; \( P < 0.001 \)) and independently higher in PrEP-eligible versus non-PrEP-eligible female participants (1.18/100 pys versus 0.50/100 pys; \( P < 0.001 \)). Among uncircumcised male participants, HIV incidence was significantly higher in PrEP-eligible versus non-PrEP-eligible participants (1.07/100 pys versus 0.27/100 pys; \( P = 0.001 \)), but there was no significant difference for circumcised male participants.

Interpretation: Implementing PrEP as a standard HIV prevention tool in generalized HIV epidemics beyond currently recognized national PrEP eligibility tool, we defined eligibility as reporting at least one of the following HIV risks in the past 12 months: sexual intercourse with more than one partner of unknown HIV status; nonmarital sex act without a condom; sex engagement in exchange for money, goods, or services; or experiencing genital ulcers. We used log-binomial and modified Poisson models to estimate prevalence ratios for PrEP eligibility and HIV incidence, respectively.

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Interpretation: Implementing PrEP as a standard HIV prevention tool in generalized HIV epidemics beyond currently recognized

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high-risk key populations could further reduce HIV acquisition and aid epidemic control efforts.

**Key Words:** HIV, cohort, HIV prevention, pre-exposure prophylaxis, PrEP, antiretroviral therapy, Africa

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INTRODUCTION

The World Health Organization (WHO) recommends pre-exposure prophylaxis (PrEP) in populations with an annual HIV infection incidence greater than 3% (substantial risk), and the President’s Emergency Plan for AIDS Relief policy for HIV services in sub-Saharan Africa prioritizes PrEP for specific key populations (ie, groups that meet the overall WHO recommendation for PrEP).1,2 PrEP has been a significant addition to the biomedical prevention options available to HIV-negative individuals at substantial risk of acquiring HIV.3–5 At least 3 million individuals in Africa are likely to be eligible for PrEP according to the WHO’s criteria.6 The annual number of new HIV infections globally has halved from its peak of 3.4 million in 1996 to 1.7 million in 2019 but has failed to meet the 2020 target of fewer than 500,000 annual new infections.7–9 Of the approximately 5000 new HIV infections occurring globally each day, approximately 61% are in sub-Saharan Africa.9 Therefore, there is an urgent need for innovative ways to lower the rate of new infections further.

PrEP, as one of the current HIV prevention tools, has contributed to a significant reduction in HIV incidence rates among key populations (men who have sex with men, female sex workers, and transgender females) and priority populations (sero-discordant couples).3,10–13 In Uganda, the Ministry of Health aims to target PrEP services using the following eligibility criteria: discordant sexual relationship [especially if the HIV-positive partner is not on antiretroviral therapy (ART), has been on ART for less than 6 months, or is not virally suppressed]; recurrent postexposure prophylaxis (PEP) users (ie, requiring PEP use more than 3 times a year); persons with multiple sexual partners of unknown HIV status in the past 6 months; persons who have had anal sexual intercourse in the past 6 months; persons engaged in sex work; persons who reported injection drug use in the past 6 months; persons with more than one episode of a sexually transmitted infection within the past 12 months; or members of key or priority populations who are unable or unwilling to consistently use condoms.14

PrEP could also be a potential HIV prevention strategy in generalized epidemic settings if targeted to persons with substantial HIV risk within these communities.15,16 In Uganda, where the annual HIV incidence is estimated at 0.46% among female individuals, 0.35% among male individuals, and 0.40% overall, there are individuals outside recognized key and priority population groups who have a significantly higher HIV risk and could benefit from PrEP. The 2016 Uganda Population-Based HIV Impact Assessment, a household-based national survey, found that nearly two-thirds of adults who reported sexual intercourse with a nonmarital, noncohabitating partner in the 12 months preceding the survey reported not using a condom during their last sexual intercourse activity with such partner.17 All individuals who reported meeting the latter criteria would have been eligible based on national PrEP eligibility criteria (which were developed after the Uganda Population-Based HIV Impact Assessment survey ended and were only implemented in key and priority populations).

PrEP is largely applied in key populations, in both developed and developing countries. In sub-Saharan Africa, there have been attempts to experiment PrEP implementation in general population settings, such as the fishing communities in Uganda and Kenya that are identified as key high-risk HIV populations.18–20 The Sustainable East Africa Research in Community Health (SEARCH) study conducted in 2016–2017 was one of the first to attempt population-level PrEP service delivery. The SEARCH study successfully performed a nonsexual behavior–based HIV risk assessment and offered PrEP services to individuals in the general population with HIV risk behavior.21,22 Thereafter, some other sub-Saharan countries attempted to provide PrEP services to their general populations. Eswatini started a country-wide randomized demonstration project in 2017,23 and Kenya expanded its PrEP services to the general population beyond the key HIV population and hotspots in 2018.16,24 Despite these initial implementation efforts, there is limited data on the number of people currently eligible for PrEP in the general population and little quantification of HIV risk associated with such population-level PrEP eligibility. In addition, questions remain about how to identify those at greatest need within generalized epidemic settings and how to best deliver PrEP to them.3,6,25,26

Based on Uganda’s national PrEP eligibility tool, we estimated the prevalence of PrEP eligibility and associated HIV risk in the low HIV incidence general population of the Rakai Community Cohort Study (RCCS), conducted by the Rakai Health Sciences Program in Rakai, Uganda. At the time the data were collected, PrEP eligibility assessments and provisions were not being implemented beyond key and priority populations in Uganda.

METHODS

The RCCS is an open, population-based community cohort study that has been previously described.25,27,28 It conducts a household census to enumerate all household residents and household-level characteristics. Residents aged 15–49 years consent to confidential individual interviews on demographics, sexual behaviors, HIV treatment, and male circumcision status. The interviews are conducted in private by trained study interviewers in community hubs that use individual tents to provide privacy or in participants’ homes. Free HIV testing services are provided; HIV status is determined using a validated 3 rapid HIV test algorithm and later confirmed with laboratory-based testing.25,28 Referrals are provided for appropriate HIV intervention services, including male circumcision, HIV testing and counseling, risk reduction behavior interventions for HIV-negative participants, and HIV treatment and viral load testing for HIV-positive participants. Since 2004, the President’s Emergency Plan for AIDS Relief has provided funding to implement HIV
services. The first RCCS survey was conducted in 1994, and 18 survey rounds (each lasting 12–18 months) have been completed by June 2018. Demographically, the survey comprises rural agrarian and rural trading communities, and fishing communities on Lake Victoria. The fishing communities are regarded as key populations for HIV intervention programs in Uganda because of their high HIV incidence and prevalence, whereas the agrarian and trading communities are regarded as generalized HIV epidemic communities with declining HIV incidence and therefore receive standard HIV intervention programs. Beginning in 2016, PrEP services were offered to members of the fishing communities but not to those in the agrarian and trading communities. This study was conducted among HIV-negative participants of the agrarian and trading communities of the RCCS to assess the extent of PrEP eligibility in the generalized HIV epidemic setting. This study included 3 RCCS survey rounds (16th survey: April 18, 2013–January 30, 2015; 17th survey: February 25, 2015–August 30, 2016; and 18th survey: October 3, 2016–June 25, 2018).

Assessment for PrEP Eligibility

We defined PrEP eligibility as reporting at least one of the following behaviors in the past 12 months: sexual intercourse with more than one partner of unknown HIV status; nonmarital sex act without a condom; sex engagement in exchange for money, goods, or services; or experiencing genital ulcers (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B825). These 4 responses form a subset of the total eligibility questions in Uganda’s national PrEP eligibility tool’s individual HIV risk assessment but represent all the questions from the PrEP eligibility tool that RCCS routinely asked even before the national PrEP eligibility tool was created in 2016. Uganda’s national PrEP eligibility tool included additional questions that were not available in RCCS [eg, had anal sexual intercourse in the past 6 months, injected drugs in the past 6 months, took PEP for sexual exposure to HIV in the past 6 months, had a partner who is HIV infected, had an HIV-infected partner who is not on ART, or had an HIV-infected partner who has been on ART for less than 6 months; (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B825)].

Study Population

Prevalence of PrEP eligibility was estimated among HIV-negative study participants aged 15–49 years who participated in the 18th survey round. HIV incidence was estimated among HIV-negative study participants aged 15–49 years who participated in at least 2 of the 3 survey rounds (16, 17, and 18). Study participants in survey 18 who contributed were included in both study populations if they met the eligibility criteria.

Statistical Analysis

To estimate the prevalence of PrEP eligibility, we conducted a cross-sectional analysis. We performed a descriptive analysis for meeting PrEP eligibility criteria among the participants. We described the distribution of demographic characteristics by PrEP eligibility and compared proportions using the χ² statistics. We used log-binomial regression models to estimate the prevalence ratios (PRs) and 95% confidence intervals (CIs) of PrEP eligibility. We used log-binomial multivariable regression to estimate adjusted PRs (aPRs) for PrEP eligibility, accounting for sociodemographic characteristics, HIV testing, and risk behaviors.

To estimate HIV incidence, we conducted a retrospective cohort analysis. We defined HIV incidence as seroconversion from HIV-negative status to HIV-positive status during the study period. We estimated HIV seroconversion time as the mid-date between the most recent survey round in which the participant tested HIV-negative and the subsequent survey round in which the participant tested HIV-positive. We used Poisson exact methods to compute HIV incidence rates, with corresponding 95% CIs as the ratio of the number of HIV incidence cases to person-years (pys) observed. We used modified Poisson regression with robust variance estimation to estimate adjusted HIV incidence rate ratios (aIRR)s and 95% CIs. We used the Wald test in multivariate regressions to estimate P values for the significant association of independent variables to the outcomes. We performed stratified analysis for each substantial HIV risk behavior, gender, and male circumcision status and assessed the effect modification of male circumcision status on the risk of acquiring HIV associated with PrEP eligibility. In multivariate analysis, we evaluated the association of HIV incidence with sociodemographic characteristics, HIV testing, and risk behaviors.

Research Ethics

This study was approved by the Research and Ethics Committee of the Uganda Virus Research Institute, the Ugandan Council of Science and Technology, and the Western Institutional Review Board. All participants provided informed consent to participate in the study.

RESULTS

Demographics and Study Participation

To estimate PrEP eligibility prevalence, we identified 12,764 participants aged 15–49 years who were HIV-negative during the last survey round. Most of them (53%) were female. Among male participants, 65% were circumcised. Participants were evenly distributed into the following age groups: 15–24, 25–34, and older than 35 years (Table 1). More male participants (43%) were between the ages of 15 and 24 years than female participants (40%). Female participants had more secondary or higher education (45% versus 37%); were more likely to be married (60% versus 49%) and more likely to participate in agriculture (44% versus 33%); were less likely to report more than one sex partner in the past 12 months (6% versus 33%); were more likely to have been tested for HIV in the past year (67% versus 49%); and were more likely to be aware of their HIV-
negative status (95% versus 90%) than male participants (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B825).

For the HIV incidence estimation cohort, we identified 11,363 participants aged 15–49 years who were HIV-negative during the study period and had at least one follow-up survey round, generating 17,381 follow-up visits and 30,721 pyses of observation. The study population distribution was similar to the PrEP eligibility prevalence study: 54% were female, and among male participants, 62% were circumcised. Participants were evenly distributed into the following age groups: 15–24, 25–34, and older than 35 years (Table 1).

During the study period (April 2013 and June 2018), male circumcision increased from 52% to 64% (P < 0.001) and ART coverage increased from 30% to 82% (P < 0.001). HIV incidence significantly decreased from 0.66/100 pyses in the first survey interval to 0.47/100 pyses in the second survey interval (P value = 0.026).

Prevalence and Correlates of PrEP Eligibility

Overall, 29% of study participants reported at least one substantial HIV risk behavior and thus met PrEP eligibility criteria. Male participants were more likely than female participants to report substantial HIV risk behaviors making them eligible for PrEP [32% versus 26%; P < 0.001 (Table 2)].

The prevalence of substantial HIV risk behaviors leading to PrEP eligibility included 4.8% of participants reporting sexual intercourse with more than one partner of unknown HIV status in the past 12 months; 16% reporting nonmarital sex act without a condom in the past 12 months; 10.8% reporting having sex in exchange for money, goods, or services in the past 12 months; and 5.4% reporting genital ulcers in the past 12 months. Male participants were more likely to report sexual intercourse with more than one partner of unknown HIV status in the past 12 months (9% versus 1%) and were twice as likely to report nonmarital sex act without a condom in the past 12 months (21% versus 11%) than female participants (Table 2).

Overall, 22% of participants reported one substantial HIV risk, 6% reported 2 substantial HIV risks, and 1% reported 3 substantial HIV risks. These numbers were similar in male and female participants (see Table 8, Supplemental Digital Content, http://links.lww.com/QAI/B825).

PrEP-eligible participants were more likely to be male and younger; have primary or less education; have never been married or been previously married; be a nonstudent; and have been tested for HIV more recently than non–PrEP-eligible participants (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B825).

In multivariable analysis (Table 3), PrEP eligibility significantly differed by marital status. Compared with currently married participants, those who were never married or had been previously married were twice as likely to be eligible for PrEP [(aPR = 2.42; 95% CI = 2.24 to 2.26) and (aPR = 2.60; 95% CI = 2.43 to 2.79), respectively]. Participants aware of their negative HIV status were 62% more likely to be eligible for PrEP (aPR = 1.62; 95% CI = 1.42 to 1.86). Being a student was associated with lower substantial HIV risk for PrEP eligibility (aPR = 0.30; 95% CI = 0.27 to 0.34) compared with other occupations.

HIV Incidence Associated With PrEP Eligibility

Overall, HIV incidence was 0.56/100 pyses in the study population. It was significantly higher in PrEP-eligible compared with noneligible participants (0.91/100 pyses versus 0.41/100 pyses; P < 0.001). Incidence was independently higher in PrEP-eligible versus noneligible female participants (1.18/100 pyses versus 0.50/100 pyses; P < 0.001) and male participants [0.66/100 pyses versus 0.30/100 pyses; P = 0.002 (Table 4)]. Among male participants, HIV incidence was significantly higher in PrEP-eligible versus noneligible uncircumcised male participants (1.07/100 pyses versus 0.27/100 pyses; P = 0.001) but was not significantly different among circumcised male participants [0.43/100 pyses versus 0.32/100 pyses; P = 0.413 (see Table 9, Supplemental Digital Content, http://links.lww.com/QAI/B825)].

After adjusting for age, education, marital status, occupation, and study survey round (Table 5 and see Table 4–7, Supplemental Digital Content, http://links.lww.com/QAI/B825), HIV incidence was 2 times higher in PrEP-eligible participants compared with that in noneligible participants (aIRR = 2.10; 95% CI = 1.56 to 2.82). HIV incidence was higher among PrEP-eligible female versus noneligible female participants (aIRR = 2.10; 95% CI = 1.46 to 3.02). Among uncircumcised male participants, HIV incidence was 3 times higher among PrEP-eligible versus noneligible participants (aIRR = 3.51; 95% CI = 1.56 to 7.91); whereas HIV incidence did not differ between PrEP-eligible and noneligible circumcised male participants (aIRRs = 1.33; 95% CI = 0.64 to 2.76). In sensitivity analysis, we found no evidence of secular changes in the HIV risk associated with PrEP eligibility from the improvement in coverage of HIV prevention interventions including ART use and male circumcision (P = 0.774).

DISCUSSION

Our study demonstrated that significant PrEP eligibility associated with increased HIV risk in a generalized HIV epidemic. Overall, 29% of participants met PrEP eligibility criteria. They had twice the risk of acquiring HIV than those who were not eligible for PrEP. The risk of acquiring HIV associated with PrEP eligibility increased 3-fold among uncircumcised male participants but remained unchanged among circumcised male participants. This novel study used a well-characterized cohort to estimate population-level PrEP eligibility and the associated risk of HIV acquisition in a lower-risk generalized HIV epidemic setting. It contributes knowledge in sub-Saharan Africa to estimating PrEP eligibility using independent substantial HIV risk behaviors included in common PrEP eligibility assessment tools. Previous studies have reported cumulative PrEP eligibility in specific populations without stratifying based on substantial HIV risk behaviors.3 Assessing PrEP eligibility using independent substantial HIV risk assessment
prEP Eligibility and Associated HIV Incidence

In this study, we observed gender differences in PrEP eligibility. Among male participants, we observed differences based on circumcision status in the HIV incidence associated with PrEP eligibility for each substantial HIV risk behavior. While male participants reported a higher prevalence of substantial HIV risk behaviors leading to PrEP eligibility, they had a lower increase in HIV incidence compared with female participants. This contrast in gender-specific risk implications is likely the result of significantly higher ART coverage in HIV-infected female participants, which decreases the transmission risk to males, and male circumcision. In this study, male circumcision seemed to trump an increased risk of acquiring HIV from substantial HIV risk behavior because we observed a 3-fold higher HIV incidence in uncircumcised male participants and observed no difference in circumcised male participants. Although our data suggest that uncircumcised males represent an important target group for PrEP services, circumcised males meeting PrEP criteria should not be excluded.

Our findings support the need for PrEP eligibility screening in general populations with lower HIV risk than targeted key HIV populations. Efforts to further reduce HIV acquisition and achieve epidemic control could be aided by implementing PrEP services in such lower HIV incidence settings, although the increased incidence rate among PrEP-eligible participants (0.91/100 pys) did not approach the WHO threshold of 3% annually. Our study demonstrated that questions provides additional information to guide PrEP implementation strategies so as to optimize the use of available resources. While current WHO policies prioritize PrEP services for key populations with an HIV incidence of at least 3% annually, the SEARCH study conducted in East Africa demonstrated successful population-wide implementa-

### TABLE 1. Distribution of Study Participants Included in the Analysis of PrEP Eligibility (October 2016–June 2018) and HIV Incidence (April 2013–June 2018) by Demographic Characteristics

| Variable                  | PrEP Eligibility Study† | HIV Incidence Study‡ |
|---------------------------|-------------------------|----------------------|
| Overall                   | 12,764                  | 17,381               |
| Sex                       |                         |                      |
| Female                    | 6793 (53%)              | 9325 (54%)           |
| Male                      | 5971 (47%)              | 8056 (46%)           |
| Age (yr)                  |                         |                      |
| 15–24                     | 5267 (41%)              | 5138 (30%)           |
| 25–34                     | 3687 (29%)              | 5747 (33%)           |
| Older than 35             | 3810 (30%)              | 6496 (37%)           |
| Education                 |                         |                      |
| None/primary              | 7517 (59%)              | 10,627 (61%)         |
| Secondary/tertiary        | 5246 (41%)              | 6754 (39%)           |
| Marital status            |                         |                      |
| Married                   | 6977 (55%)              | 10,815 (62%)         |
| Never married             | 4318 (34%)              | 4463 (26%)           |
| Previously married        | 1469 (12%)              | 2103 (12%)           |
| Occupation                |                         |                      |
| Agriculture               | 4948 (39%)              | 4011 (46%)           |
| Housework/unemployed      | 450 (4%)                | 224 (3%)             |
| Formal/government         | 930 (7%)                | 655 (7%)             |
| Alcohol trade/gambling/sex work | 207 (2%) | 133 (2%) |
| Casual labor              | 1206 (9%)               | 866 (10%)            |
| Small business            | 2116 (17%)              | 1499 (17%)           |
| Student                   | 2054 (16%)              | 833 (9%)             |
| Other                     | 853 (7%)                | 557 (6%)             |
| No. of sex partners in the last yr |         |                      |
| None                      | 2574 (20%)              | 2504 (14%)           |
| One                       | 7769 (61%)              | 11,492 (66%)         |
| Two                       | 1658 (13%)              | 2422 (14%)           |
| Three or more             | 763 (6%)                | 963 (6%)             |
| Circumcision status*      |                         |                      |
| No                        | 2075 (35%)              | 3033 (38%)           |
| Yes                       | 3896 (65%)              | 5023 (62%)           |
| Tested for HIV            |                         |                      |
| Never tested              | 892 (7%)                | 153 (1%)             |
| Tested in the last yr     | 7489 (59%)              | 9916 (57%)           |
| Tested more than 1 yr ago | 4383 (34%)              | 7312 (42%)           |
| Aware of negative HIV status |                        |                      |
| No                        | 937 (7%)                | 481 (3%)             |
| Yes                       | 11,827 (93%)            | 16,728 (97%)         |

*Only male respondents.
†Number of participants in the PrEP eligibility study.
‡Number of follow-up visits for 11,363 participants for the HIV incidence study.

### TABLE 2. Prevalence of Substantial HIV Risk Behaviors for PrEP Eligibility, Overall and by Gender (October 2016–June 2018)

| Substantial HIV Risk Behavior | All (n = 12,764) | Female (n = 6793) | Male (n = 5971) | P* |
|------------------------------|-----------------|------------------|-----------------|----|
| Any substantial risk behavior (PrEP-eligible) | 28.8% (3680) | 26.1% (1774) | 31.9% (1906) | <0.001 |
| A: Had vaginal sexual intercourse with more than one partner of unknown HIV status in the past 12 months | 4.8% (614) | 1.1% (78) | 9.0% (536) | <0.001 |
| B: Had vaginal nonmarital sex without a condom in the past 12 months | 16.0% (2040) | 11.2% (764) | 21.4% (1276) | <0.001 |
| C: Had sex in exchange for money, goods, or services in the past 12 months | 10.8% (1383) | 11.5% (780) | 10.1% (603) | 0.012 |
| D: Reported genital ulcers in the past 12 months | 5.4% (695) | 7.6% (519) | 2.9% (176) | <0.001 |

*x2 P value of the difference between male and female participants with substantial HIV risk behavior.
within lower HIV risk population settings, PrEP eligibility tools can be used to identify persons at significantly increased HIV risk who would benefit from PrEP.1,6,32 Expanding PrEP services to high-risk individuals in general populations of sub-Saharan Africa could have a major impact on the epidemic by addressing 72% of HIV cases estimated to arise outside the key and priority population groups currently offered PrEP.7 Accurately estimating population size for PrEP eligibility and priority implementation of PrEP services based on the highest estimated number of HIV cases averted will maximize PrEP’s epidemic impact.33 Accurate estimates will also provide for the PrEP coverage necessary to avert new HIV infections and allow for accurate pricing of PrEP implementation to achieve the expected impact.34–36 Sub-Saharan countries that have completed population-based demonstration projects of PrEP acceptability and uptake will need to develop population-size estimates for the expected number of persons who are eligible for the service.16,20,23,37

To maximize the benefits for PrEP in generalized HIV epidemic settings, effective screening, broad uptake, and good adherence to PrEP will be necessary. Therefore, identifying and addressing existing barriers to PrEP uptake and retention will be necessary to achieve the benefits of PrEP in programs among the broader population. Poor retention after PrEP uptake has been highlighted as the leading barrier to effectiveness.33 Long-acting PrEP, which has been developed as a potential remedy to poor retention, has now been shown to be more effective than daily oral PrEP among men having sex with men, transgender women, and cisgender women.38–40 Additional potential challenges include the stigma associated with responding to PrEP screening questions, adequately scaling up of PrEP services to be accessed for all who need them, and adequate training of health workers.22,41 These can be addressed when PrEP programs are tailored to specific communities to achieve the best client user experiences, as has been conducted in key high-risk HIV populations. Adequate training of health workers in the administration of the screening tools and of PrEP services to avert stigmatized service delivery is essential. Ideally, the general population should be first sensitized on benefits of PrEP screening tools to encourage PrEP uptake, and PrEP services should be designed to include males who report that they feel stigmatized at health care facilities.15,42–44

To achieve broad uptake of PrEP, innovative approaches such as promoting of self-identification for substantial HIV risk that requires PrEP services through mass sensitization of the general population should be considered. This approach could

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**TABLE 3. Demographic Characteristics Associated With PrEP Eligibility (October 2016–June 2018)**

| Variable                        | Substantial HIV risk (PrEP eligibility) % (n/N) | uPR (95% CI) | P         | aPR (95% CI) | P         |
|---------------------------------|-----------------------------------------------|--------------|-----------|--------------|-----------|
| Sex                             |                                               |              |           |              |           |
| Female                          | 26.1% (1774/6793)                             | Ref          | <0.001    | Ref          | <0.001    |
| Uncircumcised male              | 31.2% (648/2075)                              | 1.20 (1.11 to 1.29) | 1.12 (1.04 to 1.21) |
| Circumcised male                | 32.3% (1258/3896)                             | 1.24 (1.16 to 1.31) | 1.11 (1.04 to 1.19) |
| Age (yr)                        |                                               |              |           |              |           |
| 15–24                           | 32.2% (1696/5267)                             | Ref          | <0.001    | Ref          | <0.001    |
| 25–34                           | 30.2% (1112/3687)                             | 0.94 (0.88 to 1.00) | 0.92 (0.85 to 0.98) |
| Older than 35                   | 22.9% (872/3810)                              | 0.71 (0.66 to 0.76) | 0.68 (0.62 to 0.74) |
| Education                       |                                               |              |           |              |           |
| None/primary                    | 31.0% (2333/7517)                             | Ref          | <0.001    | Ref          | 0.003     |
| Secondary/tertiary              | 25.7% (1347/5246)                             | 0.83 (0.78 to 0.88) | 0.92 (0.86 to 0.97) |
| Marital status                  |                                               |              |           |              |           |
| Married                         | 19.9% (1385/6977)                             | Ref          | <0.001    | Ref          | <0.001    |
| Never married                   | 36.2% (1563/4318)                             | 1.82 (1.71 to 1.94) | 2.42 (2.24 to 2.60) |
| Previously married              | 49.8% (732/1469)                              | 2.51 (2.34 to 2.69) | 2.60 (2.43 to 2.79) |
| Occupation                      |                                               |              |           |              |           |
| Agriculture                     | 29.0% (1433/4948)                             | Ref          | <0.001    | Ref          | <0.001    |
| Housework/unemployed            | 26.1% (120/450)                               | 0.92 (0.79 to 1.08) | 0.81 (0.69 to 0.95) |
| Formal/government               | 25.4% (236/930)                               | 0.88 (0.78 to 0.99) | 0.94 (0.83 to 1.05) |
| Alcohol trade/gambling/sex work | 41.1% (85/207)                                | 1.52 (1.20 to 1.68) | 1.28 (1.09 to 1.50) |
| Casual labor                    | 39.9% (481/1206)                              | 1.38 (1.27 to 1.49) | 1.04 (0.96 to 1.13) |
| Small business                  | 33.0% (698/2116)                              | 1.14 (1.06 to 1.23) | 1.04 (0.97 to 1.12) |
| Student                         | 15.4% (317/2054)                              | 0.53 (0.48 to 0.60) | 0.30 (0.27 to 0.34) |
| Other                           | 36.3% (310/853)                               | 1.25 (1.14 to 1.39) | 1.03 (0.94 to 1.13) |
| Aware of negative HIV status    |                                               |              |           |              |           |
| No                              | 18.4% (172/937)                               | Ref          | <0.001    | Ref          | <0.001    |
| Yes                             | 27.9% (350/11,827)                            | 1.62 (1.41 to 1.85) | 1.62 (1.42 to 1.86) |

uPR, univariate prevalence ratio; aPR, adjusted prevalence ratio.
Type of substantial HIV risk: A = had vaginal sexual intercourse with more than one partner of unknown HIV status in the past 12 months; B = had vaginal sexual intercourse without a condom in the past 12 months; C = had sex in exchange for money, goods, or services in the past 12 months; D = experienced genital ulcers in the past 12 months.

Overall 172/30,721 0.56 (0.48 to 0.65) 112/16,346 0.69 (0.56 to 0.82) 60/14,375 0.42 (0.32 to 0.54)

### Table 4. HIV Incidence Associated With PrEP Eligibility by Gender (April 2013–June 2018)

| Overall | Female | Male |
|---------|--------|------|
| Incident Cases/Person yr (pys) | Incidence Per 100 pys (95% CI) | P | Incident Cases/Person yr (pys) | Incidence Per 100 pys (95% CI) | P | Incident Cases/Person yr (pys) | Incidence Per 100 pys (95% CI) | P |
| Overall | 172/30,721 | 0.56 (0.48 to 0.65) | | 112/16,346 | 0.69 (0.56 to 0.82) | <0.001 | 60/14,375 | 0.42 (0.32 to 0.54) | |

| PrEP eligibility status | No | Yes |
|-------------------------|----|-----|
| No | 89/21,615 | 83/9106 |
| Yes | 122/25,800 | 50/4921 |

Type of substantial HIV risk: A = had vaginal sexual intercourse with more than one partner of unknown HIV status in the past 12 months; B = had vaginal sexual intercourse without a condom in the past 12 months; C = had sex in exchange for money, goods, or services in the past 12 months; D = experienced genital ulcers in the past 12 months.

shift a substantial proportion of PrEP screening from service providers to the general population and would have the potential to reach hard-to-reach populations. Similarly, decentralization of PrEP services to facilitate easy access may improve PrEP uptake. Such a screening tool can be adapted within HIV programs and clinic settings, where staff could be trained in its use and on unthreatening interviewing techniques.

Our study suggests that there is merit to expanding the current PrEP WHO guidelines to include populations with an HIV incidence ≥3% to identify subpopulations within them who might otherwise be missed and to further reduce HIV burdens, including in populations that have made substantial reductions in HIV incidence but fail to completely eradicate transmission.

The PrEP eligibility screening tool we used was not sufficient to identify all persons at risk of HIV because we observed HIV incidence cases among the PrEP noneligible. Therefore, there is room for new screening criteria to achieve higher sensitivity in determining PrEP eligibility. For example, it is possible that adding STI testing to the screening criteria would add value to identifying PrEP eligible persons in generalized HIV epidemics.

The nonzero HIV incidence among non–PrEP-eligible persons suggests that PrEP programs should be flexible to offer PrEP to persons who perceived themselves to be at risk despite not meeting the PrEP screening criteria. Such self-identifying individuals could be sitting secondary risk that would not otherwise count as substantial HIV risk in the standard screening.

This study had several limitations. As a retrospective cohort study, although we observed that PrEP eligibility was associated with higher HIV incidence rates, we were unable to control for unobserved confounding factors, such as the HIV status and sexual behaviors of study participants’ sex partners. We were unable to adjust for the number of coital acts, which could have affected the observed relative differences in HIV incidence risk ratios observed in the study. Our results could be subject to social desirability bias, including the possibility that female participants were less likely to correctly report HIV behavioral risk factors, such as transactional sex, than male participants and were thus less likely to be deemed PrEP eligible.

Our study findings could also have been subject to recall bias. HIV risk assessment questions used to assess PrEP eligibility in our study queried HIV risk exposures over the past 12 months, compared with those over 6 months in Uganda’s national PrEP eligibility assessment tool. Thus, we may have overestimated PrEP eligibility in our analysis, compared with what national criteria would have identified. In addition, our risk assessment questions had slight differences from those in the national PrEP eligibility tool, which could have led to misclassifying participants for eligibility. Our study’s risk assessment questions did not cover the entire breadth of Uganda’s national PrEP eligibility tool, so we have likely underestimated total PrEP eligibility because Uganda’s national eligibility tool included additional questions such as: in the past 6 months, did you have anal sexual intercourse, inject drugs, take PEP for sexual exposure to HIV, or have an HIV-infected partner who had not been on ART for at least 6 months? Our cohort may not be representative of Uganda’s entire population regarding HIV risks. PrEP use information was not collected during the study. Our study was largely...
TABLE 5. HIV Incidence Rate Ratios Associated With PrEP Eligibility by Gender and Circumcision Status (April 2013–June 2018)

| Gender, Male Circumcision, and PrEP Eligibility Status | uIRR (95% CI) | P   | aIRR (95% CI) | P   |
|------------------------------------------------------|--------------|-----|--------------|-----|
| Overall (female and male)                            |              |     |              |     |
| Not eligible for PrEP                                |              |     |              |     |
| Eligible for PrEP                                    | 2.21 (1.64 to 2.99) | <0.001 | 2.10 (1.56 to 2.82) | <0.001 |
| Female                                               |              |     |              |     |
| Not eligible for PrEP                                |              |     |              |     |
| Eligible for PrEP                                    | 2.36 (1.63 to 3.42) | <0.001 | 2.10 (1.46 to 3.02) | <0.001 |
| Male                                                 |              |     |              |     |
| Not eligible for PrEP                                |              |     |              |     |
| Eligible for PrEP                                    | 2.19 (1.32 to 3.64) | 0.002  | 2.08 (1.23 to 3.54) | 0.006  |
| Male, uncircumcised only                             |              |     |              |     |
| Not eligible for PrEP                                |              |     |              |     |
| Eligible for PrEP                                    | 3.99 (1.84 to 8.66) | <0.001 | 3.51 (1.56 to 7.91) | 0.002  |
| Male, circumcised only                               |              |     |              |     |
| Not eligible for PrEP                                |              |     |              |     |
| Eligible for PrEP                                    | 1.34 (0.66 to 2.72) | 0.413  | 1.33 (0.64 to 2.76) | 0.438  |

uIRR, univariate incidence rate ratio; aIRR, adjusted incidence rate ratio.

CONCLUSIONS

A substantial number of persons are eligible for PrEP in low-risk generalized HIV epidemic population settings, and such persons can be identified using the same HIV risk assessment tools as those currently used in key HIV populations. Implementing PrEP screening and provisions in general sub-Saharan Africa populations could substantially reduce HIV incidence, beyond what has already been achieved by implementing PrEP in key populations.

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