OPEN

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

Victor Ssempijja, ScM,[a,b] Gertrude Nakigozi, MD, PhD,[b] Robert Ssekubugu, Msc,[b] Joseph Kagaayi, MD, PhD,[b] Godfrey Kigozi, MD, PhD,[b] Fred Nalugoda, Msc, PhD,[b] Betty Nantume, MA,[b] James Batte, MA, MPH,[b] Grace Kigozi, MPH,[b] Ping Teresa Yeh, MPH,[c] Hadijja Nakawooya, Bstat,[b] David Serwadda, MD, MPH,[b,d] Thomas C. Quinn, MD, MPH,[e,f] Ronald H. Gray, MD,[b,g] Maria J. Wawer, MD,[b,g] Kate M. Grabowski, Msc, PHD,[b,h] Larry W. Chang, MD, MPH,[b,c,g,e] Anja van't Hoog, MD, PhD,[i] Frank Cobelens, MD, PhD,[i] and Steven J. Reynolds, MD, MPH[b,e,f]

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 0.41/100 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

Received for publication July 1, 2021; accepted November 4, 2021.

From the [a]Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, Frederick, MD; [b]Rakai Health Sciences Program, Entebbe, Uganda; [c]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [g]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [d]Makerere University School of Public Health, Kampala, Uganda; [e]Division of Infectious Diseases, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD; [f]Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD; [h]Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD; and [i]Amsterdam Institute for Global Health and Development, Amsterdam University Medical Centers, Amsterdam, the Netherlands.

Supported by the National Institute of Allergy and Infectious Diseases (Grant numbers U01AI100031, U01AI075115, R01AI110324, R01AI102939, R01AI128779, R01AI123002, and K01AI125086). This project was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health (AI001040). This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E, and Contract No. 75N910D00024, Task Order No. (TBD) or HHSN261201500003I, Task Order No. (TBD).75N91019F00131. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government. Support for HIV care and treatment was provided by The President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (cooperative agreement number NU2GGH000817).

The authors have no conflicts of interest to disclose.

V.S. and S.J.R. led conceptualization and design of the study. V.S. analyzed and interpreted data and wrote the manuscript. R.S., J.K., G.K., F.N., B.N., J.B., G.K., P.T.Y., H.N., D.S., T.C.Q., R.H.G., M.J.W., M.K.G., L.W.C., and S.J.R. provided oversight for study coordination, data collection, and laboratory testing. A.V.H., F.C., and S.J.R. supported concept development, data interpretation, and manuscript editing. All authors participated in data interpretation, manuscript revisions, and final manuscript approval.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

De-identified data that underlie the results reported in this article can be requested through the corresponding author for approved research concepts.

Correspondence to: Victor Ssempijja, ScM, Biostatistician III, Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, 2190 Kampala Place, Dulles, VA 20189 (e-mail: victor.ssempijja@nih.gov).

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

(*J Acquir Immune Defic Syndr* 2022;90:291–299)

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.[7,8] 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.[29] 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 urban trading communities, and fishing communities on Lake Victoria.[28] The fishing communities are regarded as key populations for HIV intervention programs in Uganda because of their high HIV incidence and prevalence,[30] whereas the agrarian and trading communities are regarded as generalized HIV epidemic communities with declining HIV incidence and therefore receive standard HIV intervention programs.[25] Beginning in 2016, PrEP services were offered to members of the fishing communities but not to those in the agrarian and trading communities.[31] 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 χ^2 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 sero-conversion from HIV-negative status to HIV-positive status during the study period. We estimated HIV sero-conversion 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 (aIRRs) 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 pys 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 pys in the first survey interval to 0.47/100 pys 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 pys in the study population. It was significantly higher in PrEP-eligible compared with noneligible participants (0.91/100 pys versus 0.41/100 pys; $P < 0.001$). Incidence was independently higher in PrEP-eligible versus noneligible female participants (1.18/100 pys versus 0.50/100 pys; $P < 0.001$) and male participants [0.66/100 pys versus 0.30/100 pys; $P = 0.002$ (Table 4)]. Among male participants, HIV incidence was significantly higher in PrEP-eligible versus noneligible uncircumcised male participants (1.07/100 pys versus 0.27/100 pys; $P = 0.001$) but was not significantly different among circumcised male participants [0.43/100 pys versus 0.32/100 pys; $P = 0.413$ (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

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

*χ^2 *P* value of the difference between male and female participants with substantial HIV risk behavior.

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 implementation of PrEP services as an added tool to further reduce HIV incidence levels.[22]

In addition, 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.[25] 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

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	26.7% (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)	1.42 (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	29.7% (3508/11,827)	1.62 (1.41 to 1.85)		1.62 (1.42 to 1.86)	

uPR, univariate prevalence ratio; aPR, adjusted prevalence ratio.

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.[31] 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

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/pys	Incidence Per 100 pys (95% CI)	*P*	Incident Cases/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)		60/14,375	0.42 (0.32 to 0.54)	
PrEP eligibility status									
No	89/21,615	0.41 (0.33 to 0.51)	<0.001	60/11,951	0.50 (0.38 to 0.65)	<0.001	29/9665	0.30 (0.20 to 0.43)	0.002
Yes	83/9106	0.91 (0.73 to 1.13)		52/4396	1.18 (0.88 to 1.55)		31/4710	0.66 (0.45 to 0.93)	
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 nonmarital sex act 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 mo									
A									
No	155/29,296	0.53 (0.45 to 0.62)	0.001	105/16,219	0.65 (0.53 to 0.78)	<0.001	50/13,078	0.38 (0.28 to 0.50)	0.043
Yes	17/1424	1.19 (0.70 to 1.91)		7/128	5.49 (2.21 to 11.31)		10/1297	0.77 (0.37 to 1.42)	
B									
No	122/25,800	0.47 (0.39 to 0.56)	<0.001	80/14,518	0.55 (0.44 to 0.69)	<0.001	42/11,282	0.37 (0.27 to 0.50)	0.113
Yes	50/4921	1.02 (0.75 to 1.34)		32/1828	1.75 (1.20 to 2.47)		18/3093	0.58 (0.34 to 0.92)	
C									
No	146/27,928	0.52 (0.44 to 0.61)	0.007	94/14,751	0.64 (0.51 to 0.78)	0.026	52/13,177	0.39 (0.29 to 0.52)	0.165
Yes	26/2793	0.93 (0.61 to 1.36)		18/1595	1.13 (0.67 to 1.78)		8/1197	0.67 (0.29 to 1.32)	
D									
No	148/28,393	0.52 (0.44 to 0.61)	<0.001	97/14,728	0.66 (0.53 to 0.80)	0.169	51/13,666	0.37 (0.28 to 0.49)	0.001
Yes	24/2324	1.03 (0.66 to 1.54)		15/1615	0.93 (0.52 to 1.53)		9/709	1.27 (0.58 to 2.41)	

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.[45] 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.[25]

The PrEP eligibility screening tool we used was not sufficient to identify all persons at risk of HIV because we observed HIV incident 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 siting 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.[46,47] 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	Ref	—	Ref	—
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	Ref	—	Ref	—
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	Ref	—	Ref	—
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	Ref	—	Ref	—
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	Ref	—	Ref	—
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.

conducted in a rural setting, which may show rather different substantial HIV risk patterns from urban settings, leading to differential PrEP eligibility at the country level.

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.

ACKNOWLEDGMENTS

The authors thank the Rakai Community Cohort study participants, staff, and local community leaders who have made this study possible.

REFERENCES

1. FHI360.org. *Preparing for Prevention: Key Populations Can Lead the Way*; 2017. Available at: https://www.fhi360.org/sites/default/files/media/documents/linkages-newsletter-july2017.pdf. Accessed October 4, 2020.
2. World Health Organization. *WHO Implementation Tool for Pre-exposure Prophylaxis (Prep) of HIV Infection*; 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/279834/WHO-CDS-HIV-18.10-eng.pdf. Accessed October 15, 2020.
3. Picard J, Jacka B, Hoj S, et al. Real-world eligibility for HIV pre-exposure prophylaxis among people who inject drugs. *AIDS Behav*. 2020;24:2400–2408.
4. White E, Dunn DT, Desai M, et al. Predictive factors for HIV infection among men who have sex with men and who are seeking PrEP: a secondary analysis of the PROUD trial. *Sex Transm Infect*. 2019;95:449–454.
5. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016;387:53–60.
6. Cowan FM, Delany-Moretlwe S, Sanders EJ, et al. PrEP implementation research in Africa: what is new? *J Int AIDS Soc*. 2016;19(suppl 6):21101.
7. UNAIDS. *Joint United Nations Programme on HIV/AIDS (UNAIDS) Fact Sheet 2020*. Available at: https://www.unaids.org/en/resources/fact-sheet. Accessed September 2, 2020.
8. UNAIDS. *Joint United Nations Programme on HIV/AIDS (UNAIDS) Prevention Gap Report*. Available at: https://www.unaids.org/en/resources/documents/2016/prevention-gap. Accessed December 3, 2019.
9. Rupasinghe D, Kiertiburanakul S, Kamarulzaman A, et al. Early mortality after late initiation of antiretroviral therapy in the TREAT Asia HIV observational database (TAHOD) of the international epidemiologic databases to evaluate AIDS (IeDEA) Asia-Pacific. *HIV Med*. 2019;21:397–402.
10. Nikolopoulos GK, Christaki E, Paraskevis D, et al. Pre-exposure prophylaxis for HIV: evidence and perspectives. *Curr Pharm Des*. 2017;23:2579–2591.
11. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New Engl J Med*. 2010;363:2587–2599.
12. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New Engl J Med.* 2012;367:399–410.
13. Laurent C, Dembélé Keita B, Yaya I, et al. HIV pre-exposure prophylaxis for men who have sex with men in west Africa: a multicountry demonstration study. *Lancet HIV*. 2021;8:e420–e428.
14. Ministry of Health, Uganda. *Consolidated Guidelines for the Prevention and Treatment of HIV and AIDS in Uganda*. 2nd ed; 2018. Available at: http://library.health.go.ug/publications/hivaids/consolidated-guidelines-prevention-and-treatment-hiv-uganda. Accessed August 20, 2020.
15. Bärnighausen K, Matse S, Hughey AB, et al. We know this will be hard at the beginning, but better in the long term: understanding PrEP uptake in the general population in Eswatini. *AIDS care*. 2020;32:267–273.
16. AVAC. *A Snapshot of PrEP Scale-Up, Registration and Resources for Kenya*. PrEPWatch; 2020. Available at: https://www.prepwatch.org/country/kenya/. Accessed September 16, 2020.
17. Ministry of Health, Uganda. *Uganda Population Impact Survey (UPHIA) 2016-2017*; 2019. Available at: https://phia.icap.columbia.edu/wp-content/uploads/2019/07/UPHIA_Final_Report_Revise_07.11.2019_Final_for-web.pdf. Accessed September 16, 2020.

18. Grant RM, Koester KA. What people want from sex and preexposure prophylaxis. *Curr Opin HIV AIDS*. 2016;11:3–9.
19. Kuteesa MO, Quaife M, Biraro S, et al. Acceptability and predictors of uptake of anti-retroviral pre-exposure prophylaxis (PrEP) among fishing communities in Uganda: a cross-sectional discrete choice experiment survey. *AIDS Behav*. 2019;23:2674–2686.
20. Saxton PJW, McAllister SM. Enumerating the population eligible for funded HIV pre-exposure prophylaxis (PrEP) in New Zealand. *Sex Health*. 2019;16:99.
21. Mack N, Odhiambo J, Wong CM, et al. Barriers and facilitators to pre-exposure prophylaxis (PrEP) eligibility screening and ongoing HIV testing among target populations in Bondo and Rarieda, Kenya: results of a consultation with community stakeholders. *BMC Health Serv Res*. 2014;14:231.
22. Koss CA, Charlebois ED, Ayieko J, et al. Uptake, engagement, and adherence to pre-exposure prophylaxis offered after population HIV testing in rural Kenya and Uganda: 72-week interim analysis of observational data from the SEARCH study. *Lancet HIV*. 2020;7:e249–e261.
23. Clinicaltrials.gov. *PrEP Demonstration Study in Swaziland*. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03254550. Accessed September 16, 2020. Updated July 11, 2019.
24. National AIDS & STI Control Programme (NASCOP) MoH, Kenya framework for the implementation of pre-exposure prophylaxis of HIV in Kenya. 2020. Available at: https://prep.nascop.org/wp-content/uploads/2019/03/Framework-for-the-Implementation-of-Pre-Exposure-Prophylaxis-of-HIV-in-Kenya_.pdf. Accessed September 16, 2020.
25. Grabowski MK, Serwadda DM, Gray RH, et al. HIV prevention efforts and incidence of HIV in Uganda. *New Engl J Med*. 2017;377:2154–2166.
26. Justman JE, Mugurungi O, El-Sadr WM. HIV population surveys—bringing precision to the global response. *New Engl J Med*. 2018;378:1859–1861.
27. Wawer MJ, Sewankambo NK, Serwadda D, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group. *Lancet (London, England)*. 1999;353:525–535.
28. Chang LW, Grabowski MK, Ssekubugu R, et al. Heterogeneity of the HIV epidemic in agrarian, trading, and fishing communities in Rakai, Uganda: an observational epidemiological study. *Lancet HIV*. 2016;3:e388–96.
29. Ministry of Health, Uganda. *Safe Male Circumcision Policy*; 2010. Available at: http://library.health.go.ug/publications/policy-documents/safe-male-circumcision-policy. Accessed October 15, 2020.
30. Kagaayi J, Chang LW, Ssempijja V, et al. Impact of combination HIV interventions on HIV incidence in hyperendemic fishing communities in Uganda: a prospective cohort study. *Lancet HIV*. 2019;6:e680–e687.
31. Kagaayi J, Batte J, Nakawooya H, et al. Uptake and retention on HIV pre-exposure prophylaxis among key and priority populations in South-Central Uganda. *J Int AIDS Soc*. 2020;23:e25588.
32. Buchbinder SP, Glidden DV, Liu AY, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. *Lancet Infect Dis*. 2014;14:468–475.
33. Pyra MN, Haberer JE, Hasen N, et al. Global implementation of PrEP for HIV prevention: setting expectations for impact. *J Int AIDS Soc*. 2019;22:e25370.
34. Mera R, Scheer S, Carter C, et al. Estimation of new HIV diagnosis rates among high-risk, PrEP-eligible individuals using HIV surveillance data at the Metropolitan Statistical Area level in the United States. *J Int AIDS Soc*. 2019;22:e25433.
35. Siegler AJ, Mouhanna F, Giler RM, et al. The prevalence of pre-exposure prophylaxis use and the pre-exposure prophylaxis–to-need ratio in the fourth quarter of 2017, United States. *Ann Epidemiol*. 2018;28:841–849.
36. Rosenberg ES, Marcus JL. Progress and pitfalls in measuring HIV preexposure prophylaxis coverage in the United States. *Ann Epidemiol*. 2018;28:830–832.
37. Mitchell HD, Desai S, Mohammed H, et al. Preparing for PrEP: estimating the size of the population eligible for HIV pre-exposure prophylaxis among men who have sex with men in England. *Sex Transm Infect*. 2019;95:484–487.
38. HPTN. A phase 3 double blind safety and efficacy study of long-acting injectable cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected women. HIV Prevention Tirals Network (HPTN). 2020. Available at: https://www.hptn.org/research/studies/hptn084. Accessed November 27, 2020.
39. HPTN. A phase 2b/3 double blind safety and efficacy study of injectable cabotegravir compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis in HIV-uninfected cisgender men and transgender women who have sex with men (HPTN083). 2020. Available at: https://www.hptn.org/research/studies/hptn083. Accessed November 27, 2020.
40. Clement ME, Kofron R, Landovitz RJ. Long-acting injectable cabotegravir for the prevention of HIV infection. *Curr Opin HIV AIDS*. 2020;15:19–26.
41. Gombe MM, Cakouros BE, Ncube G, et al. Key barriers and enablers associated with uptake and continuation of oral pre-exposure prophylaxis (PrEP) in the public sector in Zimbabwe: qualitative perspectives of general population clients at high risk for HIV. *PLoS One*. 2020;15:e0227632.
42. Elopre L, Kudroff K, Westfall AO, et al. The right people, right places, and right practices: disparities in PrEP access among African American men, women, and MSM in the deep south. *J Acquir Immune Defic Syndr*. 2017;74:56–59.
43. Syvertsen JL, Robertson Bazzi AM, Scheibe A, et al. The promise and peril of pre-exposure prophylaxis (PrEP): using social science to inform PrEP interventions among female sex workers. *Afr J Reprod Health*. 2014;18:74–83.
44. Eakle R, Weatherburn P, Bourne A. Understanding user perspectives of and preferences for oral PrEP for HIV prevention in the context of intervention scale-up: a synthesis of evidence from sub-Saharan Africa. *J Int AIDS Soc*. 2019;22(suppl 4):e25306.
45. Mir JF, Mazarío MF, Coll P. Implementation models and access to HIV pre-exposure prophylaxis in Spain [in Spanish, English]. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2020;38:234–237.
46. Kelly CA, Soler-Hampejsek E, Mensch BS, et al. Social desirability bias in sexual behavior reporting: evidence from an interview mode experiment in rural Malawi. *Int Perspect Sex Reprod Health*. 2013;39:14–21.
47. Nnko S, Boerma JT, Urassa M, et al. Secretive females or swaggering males? an assessment of the quality of sexual partnership reporting in rural Tanzania. *Soc Sci Med*. 2004;59:299–310.