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DYNAMICS OF PRE-EXPOSURE (PrEP) ELIGIBILITY DUE TO WAXING AND WANING OF HIV RISK IN RAKAI, UGANDA

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Abstract

Background: We conducted a retrospective population-based study to describe longitudinal patterns of prevalence, incidence, discontinuation, resumption, and durability of substantial HIV risk behaviors (SHR) for PrEP eligibility.

Methods: The study was conducted among HIV-negative study participants aged 15-49 years that participated in survey rounds of the Rakai Community Cohort Study between August 2011 and June 2018. SHR was defined based on the Uganda national PrEP eligibility as either reporting sexual intercourse with >1 partner of unknown HIV status, non-marital sex without a condom or having transactional sex. Resumption of SHR meant resuming of SHR after stopping SHR, while persistence of SHR meant SHR on >1 consecutive visit. We used generalized estimation equations (GEE) with log-binomial regression models and robust variance to estimate survey-specific prevalence ratios (PR); GEE with modified Poisson regression models and robust variance to estimate incidence ratios for incidence, discontinuation, and resumption of PrEP eligibility.

Findings: Incidence of PrEP eligibility increased from 11.4/100 person-years (pys) in the 1st inter-survey period to 13.9/100 pys (adjusted incidence rate ratios (adjIRR)=1.28; 95%CI=1.10-1.30) and declined to 12.6/100 pys (adjIRR=1.06; 95%CI=0.98-1.15) in the 2nd and 3rd inter-survey periods, respectively. Discontinuation rates of SHR for PrEP eligibility were stable (ranging 34.9/100 pys to 37.3/100pys; p=0.207), while resumption reduced from 25.0/100 pys to 14.5/100pys (p<0.001). PrEP eligibility episodes lasted a median time of 20 months (IQR = 10–51).

Interpretation: PrEP use should be tailored to the dynamic nature of PrEP eligibility. Preventive-effective adherence should be adopted for assessment of attrition in PrEP programs.

INTRODUCTION

Pre-exposure prophylaxis (PrEP) for HIV prevention is intended for use during periods of substantial HIV risk, unlike anti-retroviral therapy (ART) for HIV treatment that is lifelong. Effective PrEP use has demonstrated the potential to accelerate reduction in HIV incidence at population level as part of combination HIV prevention.[1, 2] PrEP eligibility occurs at onset of substantial HIV risk. PrEP adherence, on-demand PrEP services and continuous availability of PrEP are essential for PrEP effectiveness. PrEP users can discontinue PrEP when they are no longer exposed to an increased HIV risk.[3, 4] The World Health Organization (WHO) recommends PrEP for HIV-negative persons with continuous, and frequent high risk of HIV infection, including most-at-risk populations such as sero-discordant couples, men who have sex with men, female sex workers, adolescent girls and young women, and fisherfolk.[5] PrEP has been adopted globally as a standard HIV prevention strategy in high-risk HIV settings,[6] including in southern and eastern Africa, where the burden of new infections is the greatest.[7, 8] In Uganda, where HIV prevalence among 15–49 year-olds reduced from 7.2% in 2017 to 5.5% by 2020, the Ministry of Health (MoH) began implementing a PrEP roll-out program to high-risk populations in 2017 in line with WHO guidelines using a PrEP eligibility screening tool administered for PrEP initiation.[9-12] Thereafter, participants were expected to take PrEP consistently, and their adherence was evaluated with the expectation of uninterrupted use.[13] According to the PEPFAR country operation 2022 plan for Uganda, PrEP targets for high-risk populations were achieved, limited access was reported in adolescent girls and young women (AGYW), key and vulnerable populations while priority is to implement the WHO differentiated service delivery models for PrEP, [14]

Several African settings have reported poor adherence to PrEP use based on attendance to drug-refill appointments and self-reported adherence of pill-intake, but without accounting for changes in the HIV risk profile.[13, 15] Previous work documenting the merits of accounting for the seasonal nature of PrEP eligibility promoted the "preventive-effective" adherence strategy, i.e. periodic use of PrEP aligned with periods of risk for HIV exposure over the life course.[16] Individuals and populations who may have intermittent HIV risk exposure or adhere to HIV risk reduction counseling messages and proceed to discontinue HIV risk behaviors require their adherence expectations to be preventive-effective.[16-19]

HIV prevention services also encourage clients to use multiple HIV prevention strategies concurrently, thereby modifying their HIV risk profiles to become PrEP ineligible. Understanding when and why PrEP users might suspend PrEP use based on their changing seasons of risk, is essential for delivering effective counselling on PrEP discontinuation and re-uptake, as well as providing flexible services for PrEP pickup and prescription. It is likely that some of the PrEP clients may have decided to stop PrEP because they are no longer at substantial risk, whereas others could re-start PrEP because they re-initiated substantial risk behaviors. The frequency, and time trends of changes in PrEP eligibility due to incidence, discontinuation, and resumption of substantial risk behaviors in generalized HIV populations are unknown, while their understanding would inform expectations of retention and follow-up in PrEP delivery services.[4, 20, 21]

To address questions about changes in PrEP eligibility, we conducted a retrospective population-based study using the Rakai Community Cohort Study (RCCS), conducted by the Rakai Health Sciences Program in Rakai, Uganda to describe longitudinal patterns of prevalence, incidence,

discontinuation, resumption, and durability of substantial HIV risk behaviors (SHR) for PrEP eligibility.

METHODS

Study Population

The study was conducted among HIV-negative study participants aged 15-49 years that participated in at least one of the four survey rounds of the RCCS conducted between August 2011 and June 2018. During the surveys, participants responded to SHR-focused questions as part of a comprehensive HIV risk behavior questionnaire survey tool. Study participants were categorized in three study cohorts. Cohort A included all study participants. Cohort B included study participants that participated in at least two survey rounds. Cohort C included study participants that participated in all the four survey rounds.

Study Setting

The RCCS is an open, population-based community cohort study that has been previously described.[22-24] It conducts a household census to enumerate all household residents and household-level characteristics. Residents aged 15–49 consent to confidential individual interviews on demographics, sexual behaviors, HIV treatment, and male circumcision status. Free HIV testing services are provided; HIV status is determined using a validated three rapid-HIV test algorithm and later confirmed with laboratory-based testing.[23] 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 (PEPFAR), the Uganda Ministry of Health, the Global Fund

and other international donors have provided funding to implement HIV services in Uganda. The first RCCS survey was conducted in 1994, and 19 survey rounds (each lasting 12–18 months) have been completed to date. Demographically, the survey comprises rural-agrarian and rural-urban trading communities, as well as 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,[25] while the agrarian and trading communities are regarded as generalized HIV epidemic communities with declining HIV incidence and therefore receive standard HIV intervention programs.[23] Beginning in 2017, PrEP services were offered to members of the fishing communities but not to those in the agrarian and trading communities.[13] The present 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 four survey rounds (15, 16, 17, and 18; referred to as 1st, 2nd, 3rd, and 4th respectively) of the RCCS, conducted between August 2011 and June 2018.

Substantial HIV risk behaviors (SHR) for PrEP eligibility

We defined SHR for PrEP based on the Uganda National PrEP eligibility tool 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; non-marital sex without a condom; sex in exchange for money, goods, or services; or having genital ulcers (supplementary table S1, http://links.lww.com/QAI/C32). These four responses form a subset of the questions in Uganda's national PrEP eligibility tool for individual HIV risk assessment but represent all the questions from the PrEP eligibility tool that RCCS had routinely asked even before the national PrEP eligibility tool was created in 2016. Additional questions in the national PrEP eligibility tool not

available in RCCS included: had anal sexual intercourse in the past six months, injected drugs in the past six months, took post-exposure prophylaxis (PEP) for sexual exposure to HIV in the past six months, had an HIV-positive partner not on ART, or had an HIV-positive partner who has been on ART for less than six months (supplementary table S1, http://links.lww.com/QAI/C32).

Statistical analysis

The prevalence of PrEP eligibility was assessed in cohort A as the proportion of participants reporting SHR events. All participants interviewed at a given survey round were eligible for SHR prevalence estimation. Generalized estimation equations (GEE) with log-binomial regression models and robust variance were used to estimate survey-specific prevalence ratios (PR) with corresponding 95% confidence intervals (CIs).

The incidence of PrEP eligibility was assessed in cohort B at the 2nd, 3^{rd,} and 4th surveys as initiation of SHR for the first time in the study period. Participants who participated in at least two surveys were eligible for incidence estimation. Incidence of SHR was assumed to have occurred at the mid-point of the follow-up interval between the last non-SHR survey and the SHR-incident survey. Exposure time at each survey was person-years (pys) of follow-up computed as the time between the interview date at the last non-SHR survey and the mid-point date to the interview date of the SHR-incident survey (in case of SHR incidence) or the interview date of the next non-SHR survey. SHR incidence was calculated per 100 pys and corresponding 95% CIs were computed with exact Poisson estimation methods. GEEs with modified Poisson regression models with robust variance were used to generate SHR incidence rate ratios with corresponding 95% CIs.

Discontinuation of PrEP eligibility was assessed in cohort B as reporting no SHR at a subsequent survey visit. It was calculated at the 2nd survey visit in participants that reported SHR at the 1st survey as the rate per 100 pys. Similar rates were calculated at the 3rd survey visit in participants that reported SHR at the 2nd survey and at the 4th survey visit in participants that reported SHR at the 3rd survey. Exposure time at each survey was pys of follow-up, computed as the time between the interview date at the last SHR survey and the mid-point date to the interview date of the next survey (in case of SHR discontinuation) or the interview date if SHR was sustained. Conversely, we defined persistence of PrEP eligibility as the opposite of discontinuation to estimate the rates per 100 pys of maintained PrEP eligibility for two or more consecutive survey visits. GEEs with a modified Poisson distribution, an exchangeable correlation matrix, and robust error variance were utilized to estimate unadjusted and adjusted incidence ratios with corresponding 95% CIs.

Resumption of PrEP eligibility was assessed in cohort B as resumption of SHR after discontinuation of SHR reported during the study period at the 3rd and 4th survey visits as the rate per 100 pys. At the 3rd survey visit, it was assessed among participants who reported SHR at the 1st survey and no SHR at the 2nd survey. At the 4th survey visit, it was assessed among participants who reported SHR at the 2nd survey and no SHR at the 3rd survey. Exposure time was pys of follow-up, computed as the time between the interview date at the survey of SHR discontinuation and the mid-point date to the interview date of the SHR resumption survey or the interview date of the next survey if SHR discontinuation was sustained. GEEs with a modified Poisson distribution, an exchangeable correlation matrix, and robust error variance were utilized to estimate unadjusted and adjusted PRs with corresponding 95% CIs.

Durability of SHR was assessed in cohort B as a continuous reporting of SHR or sustained SHR for consecutive surveys until a survey when no SHR was reported. Duration for a SHR episode was calculated as the time lapse from initiation of SHR in the study period to its discontinuation. Survival time of SHR episodes was calculated as the time from the interview date at survey of SHR onset until the mid-point time of the interval between the last SHR survey and first non-SHR survey, or until the end of study participation. We used Kaplan-Meier curves to estimate the survival functions of durability of PrEP eligibility, and we used the log-rank test to test significant statistical differences between Kaplan-Meier curves.

We demonstrated the longitudinal transition patterns of PrEP eligibility using lasagna plots, and the cumulative prevalence of PrEP eligibility status using stack graphs in cohort C (study participants that participated in all four survey rounds).

Research ethics

This study was approved by the Research and Ethics Committee of the Uganda Virus Research Institute's Research Ethics Committee (No: GC/127/19/11/137), the Ugandan National Council for Science and Technology (HS 540), from the Committee for Human Research at the Johns Hopkins University School of Public Health and School of Medicine (JHU NA_00069085, and the Western Institutional Review Board. All participants provided written informed consent to participate in the study.

Role of the funding source

PEPFAR contributed to data collection and provided HIV treatment and prevention services to study participants. The National Institute of Allergy and Infectious Diseases Division of

Intramural Research and the National Cancer Institute in the United States supported data analysis, study design, and writing.

RESULTS

Demographics and study participation

Table 1 shows the distribution and eligibility for study outcomes. Overall, 24,317 HIV-negative participants aged 15–49 were eligible for the study and included in cohort A**,** contributing 48,046 person-visits towards estimation of prevalence for PrEP eligibility. Among them, 12,759 participants were included in cohort B, contributing 23,729 inter-survey data pairs for estimation of incidence, discontinuation, resumption, persistence, and durability of PrEP eligibility. Lastly, 3,637 participants participated in all four surveys and were included in cohort C. Most participants (53%) were female. Males and females had comparable age distributions across 5-year bands. Females were more likely to be married (54% versus 43%) and less likely to have never married (33% versus 51%) or previously married (13% versus 6%), $p<0.001$. Both females and males had at least a primary education (97% versus 98%), but females had a higher representation of secondary/tertiary education than males (45% versus 39%, $p<0.001$). Cohort A and cohort B had similar distributions on demographic characteristics (Table 1).

Prevalence trends of PrEP Eligibility

Table 2 presents estimates for the prevalence of PrEP eligibility. Prevalence of PrEP eligibility increased steadily over the study period from 25.9% in 2012 (1st survey) to 28.8% in 2017 (4th survey). Female participants had 26.1% prevalence of PrEP eligibility compared to males with 31.6%. Prevalence of PrEP eligibility was 21.6% in ages 40-49 years, increased to its highest at 43.0% in ages 20-24 years, and then declined to 25.0% in ages 15-19 years. Prevalence of PrEP

eligibility was also highest in the previously married compared to the married or never married (47.8%, 19.7%, and 37.5% respectively). In multivariable analysis, compared to the 1st survey, prevalence of PrEP eligibility increased significantly by 11% (adjPR=1.11; 95%CI=1.07-1.15) between the 1st and 2nd survey, by 19% (adjPR=1.19; 95%CI=1.15-1.24) between the 1st and 3rd survey, and by 12% (adjPR=1.12; 95%CI=1.08-1.16) between the 1st and 4th survey. Males registered 10% higher prevalence of PrEP eligibility than females (adjPR=1.10; 95%CI=1.07-1.13). Compared to participants aged 40-49, the adjusted prevalence ratios of PrEP eligibility were significantly higher by 12% to 65% in participants aged 20-39 but lower by 24% in participants aged 15-19 years. Prevalence of PrEP eligibility also significantly differed by marital status. Compared to married participants, prevalence of PrEP eligibility was twice as high in the never-married and previously married participants (adjPR=2.28; 95%CI=2.18-2.38, and adjPR=2.49; 95%CI=2.39-2.60 respectively). Participants with primary education had 13% higher likelihood of PrEP eligibility than those with no education or with secondary/tertiary education (adjPR=1.13; 95%CI=0.91-1.10).

Incidence of PrEP Eligibility

Table 3 presents estimates for the incidence of PrEP eligibility. Incidence of PrEP eligibility increased from 11.4/100 in the 1st inter-survey period to 13.9/100 pys (adjIRR=1.20 95%CI=1.10-1.30) in the 2nd inter-survey period but was similar in the 3rd inter-survey period 12.6/100 pys (adjIRR=1.06; 95%CI=0.98-1.15). Incidence of PrEP eligibility was similar in males and females (13.9/100 pys versus 12.6/100 pys), and highest in participants of ages 15-19 and 20-24 (15.9./100 pys and 21.3/100 pys respectively) compared to older participants who had an incidence of PrEP eligibility ranging from 9.0/100 to 13.2/100 pys. Never married and previously married participants had high incidence of PrEP eligibility (20.2/100 pys and

24.2/100 pys respectively), while married participants had a substantially lower incidence of 8.8/100 pys. Incidence of PrEP eligibility did not differ by education.

Discontinuation of PrEP Eligibility

Table 4 shows results for discontinuation rates of PrEP eligibility. Discontinuation rates of PrEP eligibility were stable in the study period, ranging from 34.9/100 pys to 37.3/100 pys. Discontinuation rates of PrEP eligibility was lower in males compared to females (31.8/100 versus 41.1/100 pys; adjPR=0.87, 95% CI=0.82-0.92). Discontinuation rates of PrEP eligibility were also higher in married participants (55.5/100 pys) compared to never married (16.8/100 pys) or previously married participants (26.0/100 pys). Supplementary table S2, http://links.lww.com/QAI/C32 presents results for persistence of PrEP eligibility (inverse of discontinuation).

Resumption of PrEP Eligibility

Table 5 shows results for estimation of resumption for PrEP eligibility after discontinuation of SHR for PrEP eligibility. Resumption PrEP eligibility decreased in the study period from 25.0/100 pys to 14.5/100 pys (adjPR=0.60; 95%CI=0.51-0.71). Males and females were equally likely to resume SHR for PrEP eligibility (17.8/100 pys versus 16.9/100 pys; adjPR=1.04; 95%CI=0.86-1.26). Compared to married participants (12.7/100 pys), those who never married and who had previously married were at least twice as likely to resume SHR for PrEP eligibility (never married 33.9/100 pys; adjPR=2.45, 95% CI=1.87-3.19; previously married 32.0/100 pys; adjPR=2.59, 95% CI=2.07-3.24). Resumption of SHR for PrEP eligibility was not associated with age or education levels of participants.

Durability of PrEP Eligibility

Overall, median durability of PrEP eligibility was 20.0 months (IQR=10-51). Durability was significantly higher among males (median=25.5 months; IQR=10.5-57.5) than females (median=12.5 months; IQR=10-44.5). At 24-month follow-up after first observing SHR for PrEP eligibility, 43% of females and 49% of males maintained their SHR for PrEP eligibility. At 48-month follow-up, 25% of females versus 33% of males still had persisted with the same SHR episode. When stratified by marital status, durability was highest among the never married (median>60 months), followed by the previously married (29 months) and significantly lower in the married (12 months). At 24-month follow-up after first observing SHR for PrEP eligibility, 70% of the never married, 58% of the previously married, and 31% of the married maintained their SHR for PrEP eligibility. At 48-month follow-up, 61% of the never married, 39% of the previously married, and 12% of the married still had the same SHR episode.

Figure 1 shows that there were significant gender differences in SHR durability among the never married (p-value<0.001) and those previously married (p-value<0.001), but no differences among the married (p-value=0.761).

Transition patterns of SHR for PrEP eligibility

We used a closed cohort of 3,637 participants that participated in all 4 survey rounds to study transition of participants through PrEP eligibility states. Figure 2a visually shows the transition through different states of SHR for PrEP eligibility, while figure 2b shows the stacked number of participants at the different survey rounds. Prevalence of SHR for PrEP eligibility remained stable during the study period, but the proportion of participants with any history of PrEP eligibility consistently increased during the study.

DISCUSSION

This study found that PrEP eligibility was highly dynamic among HIV-negative men and women of reproductive age (15-49 years) in rural Uganda, providing some of the first empirical evidence of PrEP eligibility changes in sub-Saharan Africa. Participants transitioned through periods of acquisition, discontinuation, and resumption of PrEP eligibility. In addition, the study profiled risk factors associated with the respective states of PrEP eligibility to provide insight into the risk factors that influence PrEP eligibility. This study highlights the importance of adapting PrEP delivery strategies to the changing HIV risk profiles among clients targeted for HIV prevention strategies.

There was steady prevalence and incidence of PrEP eligibility over the study period. At a minimum, these trends indicate existing need for PrEP services in the study community. We did not find similar studies from sub-Saharan Africa on PrEP eligibility trends; however, constant prevalence of PrEP eligibility was reported in the United States of America among men who have sex with men over a 5-year period (2013-2017)[26]. Therefore, PrEP needs should be continuously assessed to avert increased unmet need.

In addition to steady PrEP eligibility over the study period, participants experienced substantial discontinuation of SHR for PrEP eligibility. SHR discontinuation rates were consistently high at each survey round. A comparison of data on discontinuation of PrEP eligibility and PrEP use attrition provides opportunity to differentiate PrEP use attrition due to discontinued HIV risk versus PrEP use non-adherence. For example, in this study, women, married participants, and those older than 24 years of age were more likely to discontinue SHR for PrEP eligibility, while men, previously married, never married, and young participants below 25 years exhibited more

persistence to continue SHR for PrEP eligibility. Previous research in the same study setting identified male gender, age less than 30 years, and employment like sex work, fishing and truck driving as risk factors for PrEP use attrition.[13] A combination of these findings provides an opportunity to identify true poor PrEP users. For example, males and young persons aged less than 25 years are potentially true poor PrEP adherers because they double as persistent PrEP eligible with higher PrEP use attrition, while females and persons aged over 29 years are more likely to be true good PrEP adherers because they double as more likely to discontinue SHR for PrEP eligibility with high PrEP use retention. This combination of findings on PrEP eligibility and PrEP use retention/attrition provides additional information required to accurately establish PrEP adherence challenges after accounting for existence of PrEP eligibility.

Resumption of PrEP eligibility was equally substantial at 14 to 25 resumptions per 100 pys of SHR discontinuation. This magnitude of resumption relative to the observed SHR discontinuation rate of 35 to 37 per 100 pys results is the dynamic nature of PrEP eligibility. Therefore, monitoring of adherence for PrEP use should be tailored to volatile changes in PrEP eligibility. The risk factors for resumption overlapped with the risk factors for acquisition, discontinuation, and persistence of SHR. For all outcomes, the male gender, the never married, or the previously married had significantly higher risk to acquire, discontinue and resume SHR for PrEP eligibility. These findings suggest that, in addition to the dynamic nature of PrEP eligibility, volatility of change in status of PrEP eligibility can vary for different demographic groups. Therefore, PrEP implementation should adapt to differentiated volatility of PrEP eligibility.

To inform expectations of un-interrupted PrEP use, we estimated the durability of PrEP eligibility episodes and found that the median time of PrEP eligibility at 20 months in this study

was significantly higher than previously reported median times for PrEP use retention that varied from 1.5 months to over 12 months.[13, 27-29] Additionally, our findings of risk factors for durability of PrEP eligibility significantly varied by gender and marital status, suggesting that there is variation in duration of HIV risk in individuals that require PrEP. Challenges of PrEP use adherence, access, and stigma have inspired long-acting PrEP regimens.[30-32] Prescription of such long-acting PrEP regimens may have to consider the expected durability of SHR for PrEP eligibility.

Our findings of SHR discontinuation and resumption underscore earlier reports on intentions to use or stop PrEP among PrEP users when they deem themselves to have or not have SHR, a phenomenon referred to as “seasons of risk”, “seasons of vulnerability”, or “seasons of PrEP”.[33, 34] However, some studies have conceptualized such episodes of reduced intake as indication of non-adherence to PrEP[19, 34-37] with risk of subsequent increased risk of HIV acquisition. Previous studies that have reported on resumption of PrEP use after discontinuation credit adherence boosting interventions like counselling, contact tracing, stigma reduction, and reminders, without mentioning that the same resumption could be due to resumption of SHR as found in our study.[38] Our findings re-affirm that periods of low or no SHR for PrEP eligibility can occur, and therefore it is likely that PrEP use discontinuation is in response to such low-risk episodes.

Our findings highlight the need for continuous assessment of PrEP eligibility in population-based PrEP programs to ensure adherence at critical seasons of HIV risk as suggested by the prevention-effective adherence strategy.[3, 4, 16] PrEP users must be empowered to assess their changing risk accurately over time and adhere to PrEP at such times to derive optimal benefit from the approach. Healthcare providers should evaluate whether such choices correspond to

actual reduced risk and advise them accordingly, since perceived risk does not always align with actual risk

In summary, this study establishes the dynamic nature of PrEP eligibility and thereby underscores the relevance of the prevention-effective adherence strategy. It is of interest to consider what prevention-effective adherence may mean for different populations of PrEP users, and for whom patterns of change in HIV risk levels and capacities for continuous assessment of risk may differ. Prevention-effective adherence should be individually tailored to help PrEP users make appropriate decisions about prevention regarding their risks and behaviors, as well as the timing of potential HIV exposures. Additionally, we recommend counselling tailored to prevention-effective use, explaining the rationale for discontinuing PrEP as based on risk and emphasizing continued PrEP use in circumstances of existing risk or unconfirmed risk reduction.[37, 39-42] Further, the dynamic nature of PrEP eligibility observed in this study underscores the need to emphasize other HIV prevention measures for the success of HIV prevention programs.

This study had several limitations. We were unable to consider study participants' sex partner's risk profiles in assessing periods of SHR for PrEP eligibility. However, this limitation occurs as a real-life challenge, since individuals are never completely certain of the indirect HIV risk from their sex partners to determine if they are at SHR. The HIV risk assessment questions used to assess PrEP eligibility in our study queried HIV risk exposures over the past 12 months, compared to six months in Uganda's national PrEP eligibility assessment tool. Thus, we may have overestimated PrEP eligibility and underestimated change in PrEP eligibility in our analysis, compared to 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 may have underestimated total PrEP eligibility. Our cohort may not be representative of Uganda's entire population regarding HIV risks. Our study was largely conducted in a rural setting, which may show rather different SHR patterns from urban settings, leading to differential PrEP eligibility patterns at the country level. Our study did not evaluate PrEP use because PrEP services were unavailable for the most part of the study. PrEP was first introduced to selected high risk sub-populations of the study area in 2017. Our study had long survey intervals that are likely to have influenced a higher than actual median time of durability. Finally, we acknowledge the possibility that the data may be subject to social desirability bias since the participants were reporting on a behavior they expected to be judged on by others.

CONCLUSIONS

As PrEP scale-up moves forward in sub-Saharan Africa and users begin to practice prevention-effective adherence, it will be important to understand and address the real-life challenges presented by a potentially cyclic model of medication use. This analysis takes a first step in detailing the dynamic nature of HIV risk and PrEP eligibility. PrEP implementation programs could learn from other public health programs that deal with cyclic exposure patterns such as family planning to adopt strategies that will successfully guide individuals through a risk-based PrEP use program for effective HIV prevention.

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Authors' contributions

VS and SJR led conceptualization and design of the study. VS analyzed and interpreted data and wrote the manuscript. RS, JK, GK, FN, BN, JB, GK, PTY, HN, DS, TCQ, RHG, MJW, MKG, LWC, and SJR provided oversight for study coordination, data collection, and laboratory testing. AVH, FC, and SJR supported concept development, data interpretation, and manuscript editing. All authors participated in data interpretation, manuscript revisions, and final manuscript approval.

Disclaimer

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

Data sharing statement

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

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Figure 1: Kaplan-Meier survival curves for durability of substantial HIV risk behavior for PrEP eligibility (a: Married, b: Never married c: Previously married) in Cohort B (**Cohort B**: study participants with ≥ 2 surveys)

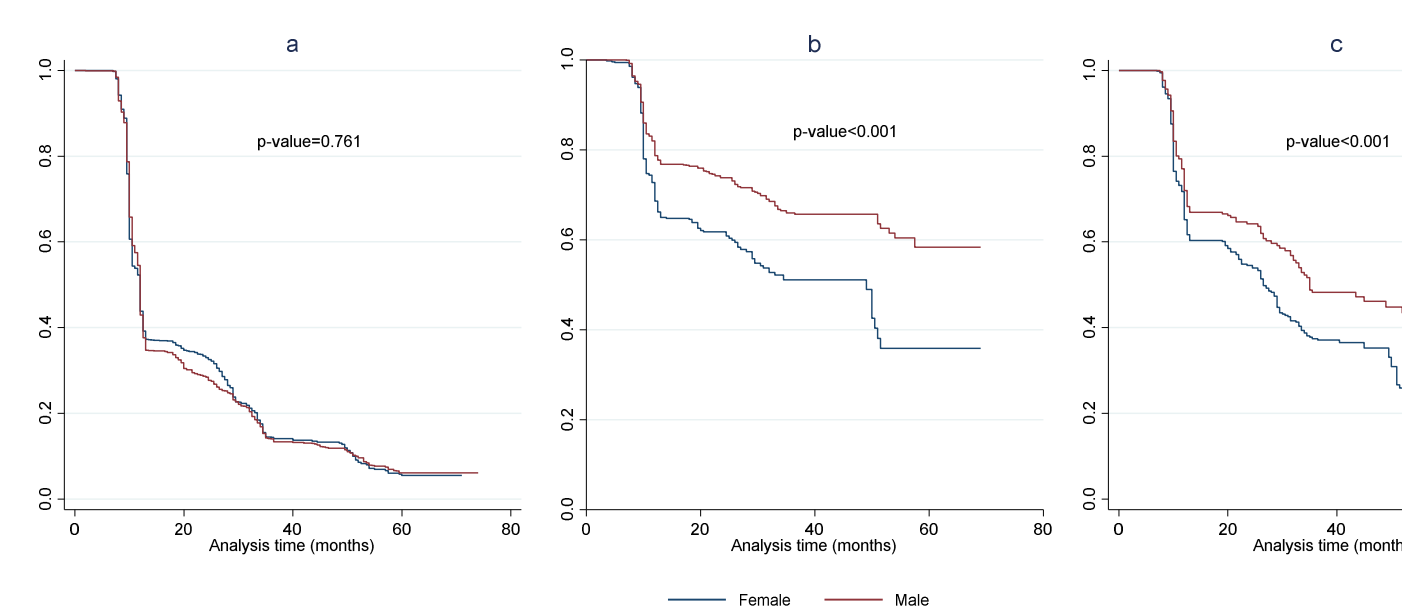

Figure 1: Kaplan-Meier survival curves for durability of substantial HIV risk behavior for PrEP eligibility (a: Married, b: N
Previously married) in Cohort B (**Cohort B**: study participants with ≥ 2 surveys)

Figure 2a: Transition patterns of Substantial HIV risk behaviors (SHR) that qualify for PrEP eligibility. Figure 2b: Stack graph for status of SHR that qualify for PrEP eligibility for the 1st, 2nd, 3rd and 4th survey rounds.

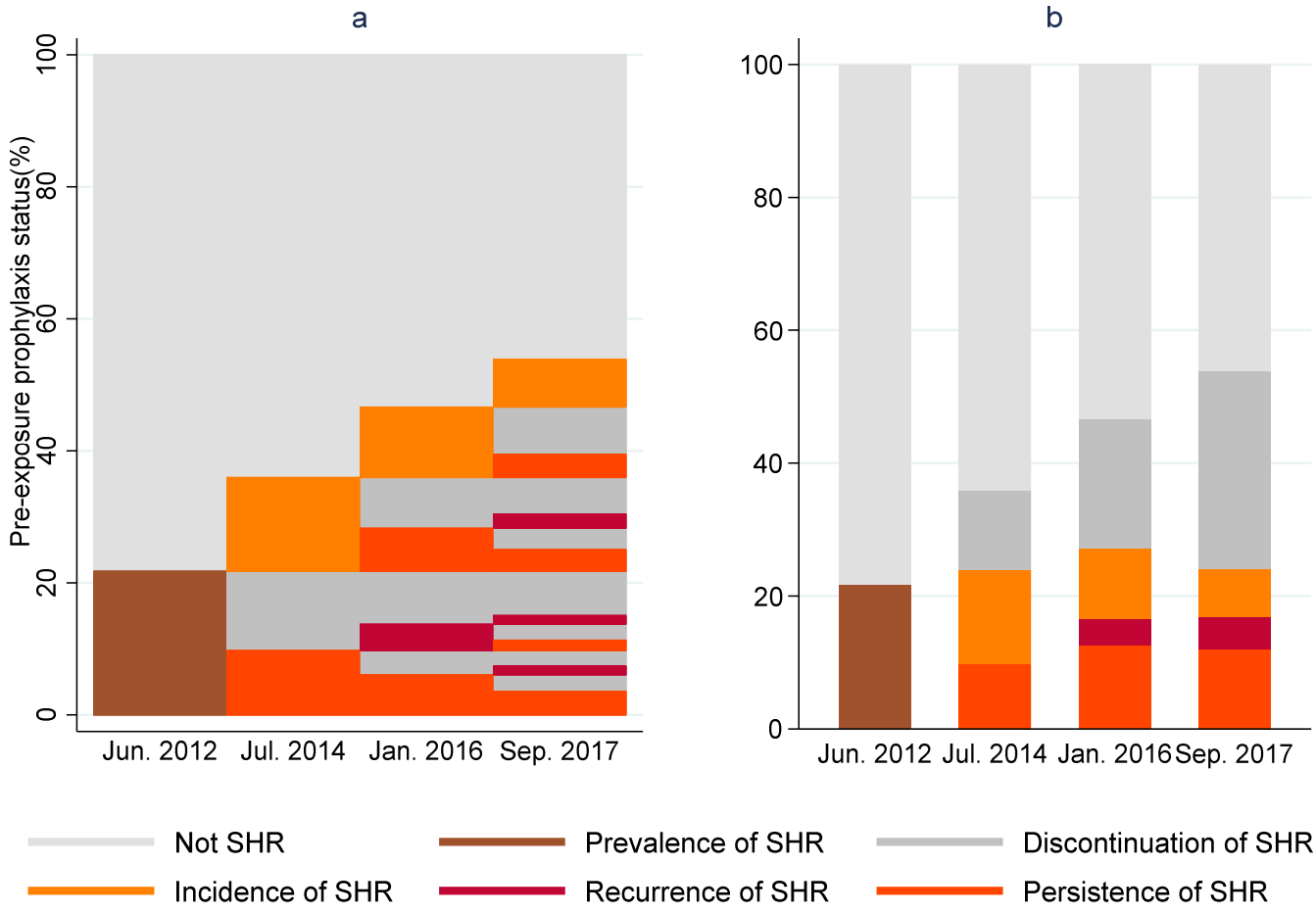

Figure 2a: Transition patterns of Substantial HIV risk behaviors (SHR) that qualify for PrEP eligibility. Figure 2b: Stack graph for status of SHR that qualify for PrEP eligibility for the 1st, 2nd, 3rd and 4th survey rounds.

Table 1: Demographic characteristics of study participants at baseline survey

Variable	Cohort A			Cohort B		
	Female N (%)	**Male N (%)**	**p-value[#]**	**Female N (%)**	**Male N (%)**	**p-value[#]**
Overall	**12883 (53%)**	**11434 (47%)**		**6678 (52%)**	**6081 (48%)**	
Survey(s) *						
1st survey	5739 (45%)	4982 (44%)		3811 (57%)	3342 (55%)	
2nd survey	2887 (22%)	2625 (23%)	0.37	1816 (27%)	1714 (28%)	0.047
3rd survey	2194 (17%)	2008 (18%)		1051 (16%)	1025 (17%)	
4th survey	2063 (16%)	1819 (16%)		-	-	
Age (years)						
40-49	1096 (9%)	1292 (11%)		688 (10%)	772 (13%)	
35-39	1162 (9%)	1094 (10%)		813 (12%)	719 (12%)	
30-34	1629 (13%)	1337 (12%)	<0.001	1078 (16%)	810 (13%)	<0.001
25-29	2091 (16%)	1763 (15%)		1206 (18%)	966 (16%)	
20-24	2778 (22%)	2104 (18%)		1291 (19%)	978 (16%)	
15-19	4127 (32%)	3844 (34%)		1602 (24%)	1836 (30%)	
Marital status						
Married	6930 (54%)	4868 (43%)		1720 (26%)	2839 (47%)	
Never married	4315 (33%)	5870 (51%)	<0.001	4137 (62%)	2863 (47%)	<0.001
Previously married	1638 (13%)	696 (6%)		821 (12%)	379 (6%)	
Education						
None	444 (3%)	259 (2%)		252 (4%)	150 (2%)	
Primary	6657 (52%)	6710 (59%)	<0.001	3575 (54%)	3699 (61%)	<0.001
Secondary/Tertiary	5782 (45%)	4464 (39%)		2851 (43%)	2232 (37%)	

Cohort A: All study participants. **Cohort B**: Study participants with ≥ 2 surveys.
[#]chi-square test of association

*Survey interview dates (median; range): 1st survey dates (Jun 2012; Aug 2011-Oct 2013), 2nd survey dates (July 2014; Apr 2013-Jan 2015), 3rd survey dates (Jan 2016; Jan 2015-Sep 2016), 4th survey dates (Sep 2017; Oct 2016-Jun 2018).