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Original Contribution

Transitions Between Preexposure Prophylaxis Eligibility States and HIV Infection in the Lisbon Cohort of HIV-Negative Men Who Have Sex With Men: A Multistate Model Analysis

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We aimed to describe transitions between preexposure prophylaxis (PrEP) eligibility and human immunodeficiency virus (HIV) infection among HIV-negative men who have sex with men (MSM). We used data from 1,885 MSM, who had not used PrEP, enrolled in the Lisbon Cohort of MSM, with at least 2 consecutive measurements of PrEP eligibility from 2014–2020. A time-homogeneous Markov multistate model was applied to describe the transitions between states of PrEP eligibility—eligible and ineligible—and from these to HIV infection (HIV). The intensities of the transitions were closer for ineligible-to-eligible and eligible-to-ineligible transitions (intensity ratio, 1.107, 95% confidence interval (CI): 1.080, 1.176), while the intensity of the eligible-to-HIV transition was higher than that for ineligible-to–HIV transition (intensity ratio, 9.558, 95% CI: 0.738, 65.048). The probabilities of transitions increased with time; for 90 days, the probabilities were similar for the ineligible-to-eligible and eligible-to-ineligible transitions (0.285 (95% CI: 0.252, 0.319) vs. 0.258 (95% CI: 0.228, 0.287)), while the eligible-to-HIV transition was more likely than ineligible-to-HIV (0.004 (95% CI: 0.003, 0.007) vs. 0.001 (95% CI: 0.001, 0.008)) but tended to become closer with time. Being classified as ineligible was a short-term indicator of a lower probability of acquiring HIV. Once an individual moved to eligible, he was at a higher risk of seroconversion, demanding a timely delivery of PrEP.

eligibility determination; HIV; men who have sex with men; multistate models; preexposure prophylaxis

Abbreviations: CI, confidence interval; E–I, eligible to ineligible; E–HIV, eligible to HIV infection; HIV, human immunodeficiency virus; I–E, ineligible to eligible; I–HIV, ineligible to HIV infection; MSM, men who have sex with men, PrEP, preexposure prophylaxis.

Preexposure prophylaxis (PrEP), the use of antiretrovirals to prevent human immunodeficiency virus (HIV) infection, is highly effective when recommended to individuals at high risk, and adherence is high (1–4). PrEP has been acknowledged as a much-needed additional prevention tool as evidence shows that, among men who have sex with men (MSM), the largest effects on HIV incidence are expected when PrEP is implemented in combination with the "test and treat" approach (5–7).

In 2015, the European Centre for Disease Prevention and Control recommended that European Union members states should consider integrating PrEP into their existing HIV prevention packages for those most at risk of HIV infection, starting with MSM (8). Portugal approved the use of tenofovir disoproxil fumarate and emtricitabine as PrEP in 2017, and it has been provided, free of charge, in public hospitals since February 2018. The Portuguese Ministry of Health issued the clinical guideline for PrEP use in November 2017, and it applies to anyone at increased risk of acquiring HIV infection (9). Increased risk was defined as 1) having had condomless sexual intercourse in the past 6 months and sexual partners with unknown HIV status, a diagnosis of a sexually transmitted infection, or use of postexposure prophylaxis for HIV; 2) having used psychoactive substances during sexual intercourse; 3) having an HIV-positive partner, without medical care, antiretroviral treatment, or viral suppression and not using condoms consistently; 4) engaging in sexual intercourse to obtain money, goods, or illicit substances and not using condoms consistently; or 5) being in situations of social vulnerability

that may expose them to unprotected sex with individuals at high risk of acquiring HIV infection (9).

Ascertainment of eligibility for PrEP was based on the report of any of the above-mentioned behavioral and clinical information. This led to a dichotomous classification of having or not having an indication for PrEP at a given time. However, it is known that sexual behaviors—including condom use, number of partners, and sexual practices, as well as life circumstances, such as a steady partnership, the HIV status of sexual partners, and their suppressive status—change with time (10–12). This implies that eligibility for PrEP based on the definition of risk behaviors will also change with time. This is also supported by PrEP users' reports of intentions to switch between PrEP regimens, indicating that they are aware that their risk of HIV may vary over time and that PrEP use may be adapted accordingly (13).

Considering this, we aimed to describe the transitions between PrEP eligibility states and from these to HIV infection by estimating the intensity and probability of those transitions among participants, who had not used PrEP, of a cohort of HIV-negative MSM in Lisbon, Portugal.

METHODS

We used data from the participants enrolled in the Lisbon Cohort of MSM, an open, noninterval, prospective cohort. Participants were recruited at CheckpointLX, a Portuguese community-based HIV voluntary counseling and testing center in Lisbon targeted at MSM and whose staff are trained peer community health workers, themselves MSM. Being a cisgender man, aged 18 years or older, reporting sex with men, and presenting a nonreactive HIV test result at baseline were criteria to be enrolled in the cohort. A detailed description of the cohort is provided elsewhere (11, 14). At each visit to CheckpointLX, peer community health workers administered a structured questionnaire and performed a rapid HIV test. Rapid tests for syphilis, hepatitis C, and hepatitis B were also offered according to an individual assessment. Endpoints for follow-up were HIV acquisition or death. Cohort recruitment started in April 2011, but this study only covers the period from March 2014 to June 2020, after a questionnaire revision considering the ability to assess eligibility for PrEP according to the Portuguese National Health Service guidelines.

All participants provided written informed consent prior to inclusion, and the study protocol was approved by the ethics committee of São João Hospital Center and Medical School, University of Porto (ID 104/12).

Study instruments and variables

We defined PrEP eligibility according to the clinical guidelines provided by the Portuguese National Health Service (9). Each criterion of the guideline was matched with the behavioral information collected at the baseline and follow-up evaluations and was operationally defined as described in Table 1. A more detailed description is available elsewhere (15). Exposure ascertainment was based on the information regarding the previous 12 months provided at the baseline visit and, thereafter, based on the period between visits. Participants were defined as eligible when they met any of the Portuguese National Health Service criteria, except for the criterion relating to "persons in situations of social vulnerability that may expose them to unprotected sex with individuals at high risk of acquiring HIV infection," for which there was not enough information collected. A response of "rather not say" or "do not know" or missing information associated with a "no" response in all the remaining criteria resulted in exclusion from the analysis.

A third-generation HIV test (Alere Determine HIV-1/2; Abbott, Vila Nova de Gaia, Portugal) was performed at each visit, except from October 2016 to October 2017, when a fourth-generation test (Alere Determine HIV-1/2 Ag/Ab Combo; Abbott) was used. In case of a reactive test result, a referral was offered to an HIV/infectious diseases clinic of a public hospital of the participant's choice, where a confirmatory test would be performed. CheckpointLX peer community health workers provided pretest and posttest counseling at every visit in an opt-out strategy.

Statistical analysis

We performed a descriptive analysis of the participants' characteristics at baseline and by state at first transition, and we compared groups using the t test for independent variables for mean age and the Pearson χ^2 test for categorical variables. These analyses were performed using SPSS for Windows, version 25.0 (SPSS Inc, Chicago, Illinois).

To describe the transitions between PrEP eligibility states (eligible and ineligible) and from these to HIV infection, we considered a 3-state model, one of which—HIV infection—was an absorbing state, as depicted in Figure 1. The 4 possible transitions are identified by the arrows: 1) ineligible to eligible (I–E), 2) eligible to ineligible (E–I), 3) ineligible to HIV infection (I–HIV), and 4) eligible to HIV infection (E–HIV). We assumed that participants might be in the ineligible or eligible states at time $t = 0$ but could be in the absorbing state only at $t = 0 + u$. Because it is impossible to observe participants continuously, the exact times of state-to-state transitions were interval-censored. Under this constraint, standard multistate methods were adapted. The multistate models were computed using the msm package in R (R Foundation for Statistical Computing, Vienna, Austria). (16) We tested a time-homogeneous Markov multistate model with the following covariates at baseline: age, country of birth (Portugal vs. others), sexual orientation (gay vs. other), previous HIV test (no vs. yes), reasons for testing (reasons related to symptoms or risk exposure vs. other reasons), and education (less than higher education vs. higher education). A non–time-homogeneous model with 1- and 2-time intensity changes ($t = 1.6$ and $t = 3.0$), a piecewise constant model, and crude time-homogeneous model were also tested. The likelihood test ratios showed that the time-homogeneous model with age, country of birth, sexual orientation, previous HIV test, and reason for the

Table 1. Operational Definition of Each Eligibility Criterion for Preexposure Prophylaxis in the Portuguese National Health Service Guidelines, 2018

PNHS Criteria	Operational Definition of Eligibility
Persons who have had condomless sex in the past 6 months and sexual partners with unknown HIV status, or . . .	Any anal sex with steady or occasional partners without a condom AND had at least 1 sexual partner for whom the HIV status was unknown
People who reported use of psychoactive substances during sexual intercourse, or . . .	Used at least 1 psychoactive substance during sex, including cannabis, heroin, cocaine, ecstasy, amphetamines, poppers, LSD, ketamine, GHB, methadone, substances sold at smart shops, methamphetamines, mephedrone, or other
Persons who have had condomless sex in the past 6 months and had an STI diagnosis, or . . .	Any anal sex with steady or occasional partners without a condom AND self-reported syphilis, chlamydia, lymphogranuloma venereum, gonorrhea, trichomoniasis, genital herpes, condyloma or genital warts, or other STI diagnosis
Persons who have had condomless sex in the past 6 months and used PEP for HIV, or . . .	Any anal sex with steady or occasional partners without a condom AND used PEP
People whose partner was infected with HIV, without medical care or ART, or without viral suppression and did not use condoms consistently, or . . .	Anal sex with a steady partner AND had at least 1 HIV-positive steady partner AND had at least 1 HIV-positive partner who was not taking treatment or whose HIV status was not known OR had at least 1 HIV-positive partner who had a detectable or unknown viral load AND any anal sex with a steady or occasional partners without a condom
People who engaged in sexual intercourse to obtain money or goods or illicit substances and do not use condoms consistently	People who reported having received money, goods, or drugs in exchange for sex AND had any anal sex with a steady or occasional partners without a condom

Abbreviations: ART, antiretroviral therapy; GHB, gamma-hydroxybutyric acid; HIV, human immunodeficiency virus; LSD, lysergic acid diethylamide; PEP, postexposure prophylaxis; PNHS, Portuguese National Health Service; STI, sexually transmitted infection.

test at baseline had the best fit. Table 2 shows the estimated adjusted hazard ratios and 95% confidence intervals (CIs) of transitions for each covariate in this model.

Multistate data can be summarized by counting, for each state s, the number of times an observation from the state r was followed by the state s. These are frequencies of pairs of consecutive observed states. The intensities for each possible transition represent the instantaneous risk of moving between the states. They were calculated by the maximum likelihood estimation and the corresponding 95% CI. We computed the 95% CI using 2 bootstrap resampling approaches: 1) a bootstrap data set was drawn by resampling pairs of consecutive states from the full data, and 2) we considered a resampling scheme based on the full trajectories of the participants. We provided 1,000 bootstrap replicates. The results showed that the CIs were narrower using the second approach; therefore, we present those results. The same bootstrap resampling plan was used to compute the CI for the ratios of the intensities from the final time-homogeneous model with covariates. The probabilities of those transitions at multiple window periods were also computed. For a time-homogeneous process, the (r, s) entry of $P(t)$, $P_{rs}(t)$ is the probability of being in state s at a time $t + u$ in the future, given that the state at time u is r. The CIs for the transition probabilities were calculated with bootstrap data sets computed by resampling independent transitions between pairs of states. Then, the CIs or standard errors for the corresponding statistic were calculated by summarizing the returned list of the replicated outputs. We used 500 resamples.

Participants

From March 2014 to June 2020, 5,167 participants were enrolled in the cohort; among those, 205 were excluded because they had used PrEP. Among the remaining participants,

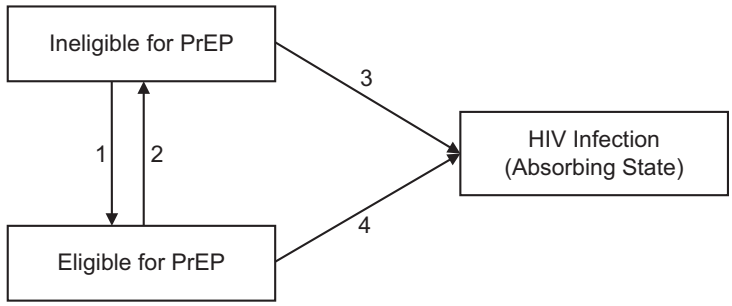

Figure 1. Model for the transition between preexposure-prophylaxis (PrEP) eligibility states (eligible and ineligible) and from these to human immunodeficiency virus (HIV) infection, Lisbon, Portugal, 2014–2020. The 4 possible transitions are identified by the arrows: 1) ineligible to eligible, 2) eligible to ineligible, 3) ineligible to HIV infection, and 4) eligible to HIV infection.

3,068 only came for the baseline visit, and 2,099 came for at least 2 visits. A comparison between participants with and without follow-up visits is presented in Table 3. Participants with follow-up visits were slightly younger and more frequently born in Portugal. There were no differences in the education level, the reported sexual orientation, previous HIV test, reasons for the baseline test, and eligibility for PrEP at baseline.

The final analysis was conducted among those participants with at least 2 visits and valid information on PrEP eligibility in at least 2 consecutive visits; therefore, we excluded 214 participants who did not meet the latter criterion. The remaining 1,885 participants had a total of 3,747.47 person-years of follow-up (median, 1.71 years; interquartile range, 2.12; range, 9 days to 6.24 years) and a median of 3 visits (interquartile range, 2; range, 2–19 visits). Among those who seroconverted, the median time of follow-up was 1.2 years (interquartile range, 2.22 years).

RESULTS

Table 4 presents the descriptions of the participants overall and by state at first transition. Overall, the median age of participants was 29.5 years (25th–75th percentiles, 23.0–35.0); no differences were found by state of the first transition. Regarding the country of birth, most participants were born in Portugal (74.1%), followed by Brazil (11.9%) and other European countries (9.0%). The proportions of participants born in Brazil or European countries besides Portugal were higher among participants at the eligible state in the first transition. Additionally, 59.3% held a higher education degree, and 83.5% self-identified as gay. No differences were found between groups for these 2 characteristics. Participants at the eligible state reported more frequently previously being tested for HIV (81.1% vs. 73.8% among those in the ineligible state) and more frequently cited risk exposure as the reason for testing (71.5% vs. 54.8%).

Table 2. Estimated Adjusted Hazard Ratios and Transitions Between Preexposure Prophylaxis Eligibility States for Each Covariate in the Final Time-Homogeneous Model, Lisbon, Portugal, 2014–2020

Covariate at Baseline	Transition							
	Ineligible to Eligible		Eligible to Ineligible		Ineligible to HIV Infection		Eligible to HIV Infection	
	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI
Age	1.026	1.004, 1.049	1.019	0.997, 1.042	1.050	0.963, 1.145	0.977	0.931, 1.026
Country of birth (Portugal vs. other country)	0.734	0.497, 1.084	1.052	0.715, 1.547	0.160	0.015, 1.704	0.667	0.282, 1.576
Reason for testing (reasons related to symptoms or risk exposure vs. other reasons)	0.608	0.433, 0.854	0.692	0.490, 0.977	0.074	0.001, 4.318	1.171	0.438, 3.129
Previous HIV test (no vs. yes)	1.186	0.880, 1.597	0.995	0.729, 1.358	0.458	0.032, 6.545	1.051	0.390, 2.835

Abbreviation: aHR, adjusted hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus.

Table 3. Baseline Characteristics of Participants With and Without Follow-up Visits in a Study of Transitions Between Preexposure Prophylaxis Eligibility States, Lisbon, Portugal, 2014–2020

Characteristic	Participants Without Follow-up ($n = 3,068$)		Participants With Follow-up ($n = 2,099$)		*P* Value
	No.	%	No.	%	
Age, years					
Mean[a]	30.1 (9.31)		29.4 (9.08)		0.012[b]
Median[c]	28 (23–35)		27 (23–34)		0.004[d]
Minimum–maximum[e]	18–77		18–69		
Country/region of origin					<0.001[f]
Portugal	2,053	67.0	1,544	73.6	
Brazil	542	17.7	261	12.4	
Other European countries	278	9.1	189	9.0	
African country	78	2.5	42	2.0	
North, Central, and South America (except Brazil)	70	2.3	43	2.0	
Asia/Middle East/Oceania	43	1.4	19	0.9	
Missing	4		1		
Educational level					>0.999[f]
Less than higher education	1,216	40.8	849	40.8	
Higher education	1,766	59.2	1,232	59.2	
Rather not say/missing	86		18		
Sexual orientation					0.329[f]
Gay	2,515	83.1	1750	83.5	
Bisexual	397	13.1	271	12.9	
Heterosexual	42	1.4	18	0.9	
Other/does not use a term/does not know	72	2.4	56	2.7	
Rather not say/missing	42		4		
Previous HIV testing					0.605[f]
No	620	20.5	442	21.1	
Yes	2,410	79.5	1,653	78.9	
Rather not say/missing	38		4		
Reason for the index test					0.464[f]
Reasons related to symptoms	208	6.9	132	6.3	
Reasons related to risk exposure	1,924	63.7	1,364	65.3	
Reasons not related to symptoms or risk exposure	887	29.4	592	28.4	
Rather not say/missing	49		11		
PNHS criteria, not mutually exclusive					
Persons who have had condomless sex in the past 6 months and sexual partners with unknown HIV status	1,208	40.6	870	41.9	0.342[f]
Missing	89		24		
People who reported use of psychoactive substances during sexual intercourse	928	31.1	616	29.7	0.288[f]
Missing	88		25		

Table continues

Table 3. Continued

Characteristic	Participants Without Follow-up ($n = 3,068$)		Participants With Follow-up ($n = 2,099$)		*P* Value
	No.	%	No.	%	
Persons who have had condomless sex in the past 6 months and had an STI diagnosis	208	7.0	152	7.3	0.737[f]
Missing	109		22		
Persons who have had condomless sex in the past 6 months and used PEP for HIV	49	1.6	35	1.7	0.995[f]
Missing	74		15		
People whose partner was infected with HIV without medical care or ART or without viral suppression and did not use condoms consistently	32	1.1	20	1.0	0.830[f]
Missing	149		81		
People who engaged in sexual intercourse to obtain money or goods or illicit substances and did not use condoms consistently	51	1.7	30	1.4	0.550[f]
Missing	59		17		
Eligible for PrEP	1,776	60.4	1,260	61.5	0.445[f]
Missing	128		51		

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PEP, postexposure prophylaxis; PNHS, Portuguese National Health Service; PrEP, preexposure prophylaxis; STI, sexually transmitted infection.

[a] Values are expressed as mean (standard deviation).

[b] *P* value (2-sided) for the *t* test for independent samples.

[c] Values are expressed as median (interquartile range).

[d] *P* value (2-sided) for the Mann-Whitney U test.

[e] Values are expressed as minimum to maximum.

[f] *P* value (2-sided) for the χ^2 test.

There were 648 transitions from ineligible to eligible, 782 from eligible to ineligible, 11 from ineligible to HIV infection, and 36 from eligible to HIV infection over 3,747.47 person-years of observation; 2,851 transitions were to the same state (1,308 in the ineligible and 1,543 in the eligible states).

Figure 2 shows the intensity and corresponding 95% CI for each transition. The estimated intensity was 10% higher (1.107, 95% CI: 1.080, 1.176) for I–E (1.587, 95% CI: 1.253, 1.647) than for E–I (1.453, 95% CI: 1.138, 1.522), while the transition E–HIV was 9.6 times higher but with a wider CI (9.558, 95% CI: 0.738, 65.048) than I–HIV (0.019 (95% CI: 0.013, 0.024) vs. 0.002 (95% CI: 0.001, 0.004)).

Table 5 presents the estimated transition probabilities and 95% CIs at multiple time points for the PrEP eligibility states and HIV infection. The transition probabilities estimated for 30 days were similar for the transitions I–E and E–I (0.120 (95% CI: 0.103, 0.138) vs. 0.109 (95% CI: 0.094, 0.125)), but the transition E–HIV was more likely than I–HIV (0.002 (95% CI: 0.001, 0.003) vs. 0.000 (95% CI: 0.000, 0.002)). The estimated transition probabilities increased with time up to a probability of 0.463 (95% CI: 0.443, 0.480) for E–I and 0.513 (95% CI: 0.491, 0.531) for I–E at 2 years. Both transitions always showed a similar probability. The transition probabilities of I–HIV and E–HIV also increased up to 0.019 (95% CI: 0.013, 0.046) and 0.025 (95% CI: 0.017, 0.045), respectively, at 2 years. The point estimate of the transition probability to HIV infection was always higher when at the eligible state but tended to become closer to that from the ineligible state over time. However, the CIs were wide and overlapped at all time points.

DISCUSSION

The probability of transitioning to HIV infection was higher at any time point from the eligible state vs. from the ineligible state but tended to become closer with time. This indicated that being defined as ineligible was only a short-

Table 4. Baseline Characteristics of Participants in a Study of Transitions Between Preexposure Prophylaxis Eligibility States, Overall and by State of the First Transition, Lisbon, Portugal, 2014–2020

Characteristic	Overall		Ineligible		Eligible		*P* Value
	No.	%	No.	%	No.	%	
Total	1,885		726	38.5	1,159	61.5	
Age, years							
Mean[a]	29.5 (9.13)		29.1 (9.09)		29.7 (9.14)		0.194[b]
Median[c]	27 (23–35)		26 (22–34)		27 (23–35)		0.090[d]
Minimum–maximum[e]	18–69		18–66		18–69		
Country/region of origin							<0.001[f]
Portugal	1,396	74.1	579	79.8	817	70.6	
Brazil	225	11.9	58	8.0	167	14.4	
Other European countries	170	9.0	57	7.9	113	9.8	
African country	40	2.1	15	2.1	25	2.2	
North, Central, and South America (except Brazil)	37	2.0	9	1.2	28	2.4	
Asia/Middle East/Oceania	16	0.8	8	1.1	8	0.7	
Missing	1		0		1		
Educational level							0.174[f]
Less than higher education	763	40.7	279	38.7	484	42.0	
Higher education	1,111	59.3	442	61.3	669	58.0	
Rather not say/missing	11		5		6		
Sexual identity							0.354[f]
Gay	1,574	83.5	617	85.0	957	82.6	
Bisexual	244	13.0	90	12.4	154	13.3	
Heterosexual	15	0.8	4	0.6	11	0.9	
Other/does not use a term/does not know	51	2.7	15	2.1	36	3.1	
Rather not say/missing	1		0		1		
Previous HIV testing							<0.001[f]
No	409	21.7	190	26.2	219	18.9	
Yes	1,475	78.3	536	73.8	939	81.1	
Rather not say/missing	1		0		1		
Reason for the index test							<0.001[f]
Related to symptoms	119	6.3	42	5.8	77	6.7	
Related to risk exposure	1,222	65.0	398	54.8	824	71.5	
Related to symptoms or risk exposure	538	28.6	286	39.4	252	21.9	
Rather not say/missing	6		0		6		

Abbreviation: HIV, human immunodeficiency virus.
[a] Values are expressed as mean (standard deviation).
[b] *P* value (2-sided) for the t test for independent samples.
[c] Values are expressed as median (interquartile range).
[d] *P* value (2-sided) for the Mann-Whitney U test.
[e] Values are expressed as minimum-maximum.
[f] *P* value (2-sided) for the χ^2 test.

term indicator of a lower probability of acquiring HIV. The intensity of transitions was, as expected, higher for E–HIV than for I–HIV but with a wide ratio CI (0.019 (95% CI: 0.013, 0.024) vs. 0.002 (95% CI: 0.001, 0.004); intensity ratio, 9.558 (95% CI: 0.738, 65.048)). On the other side, the intensities of transitions I–E and E–I were similar (1.587 (95% CI: 1.253, 1.647) vs. 1.453 (95% CI: 1.138, 1.522); intensity ratio, 1.107 (95% CI: 1.080, 1.176)).

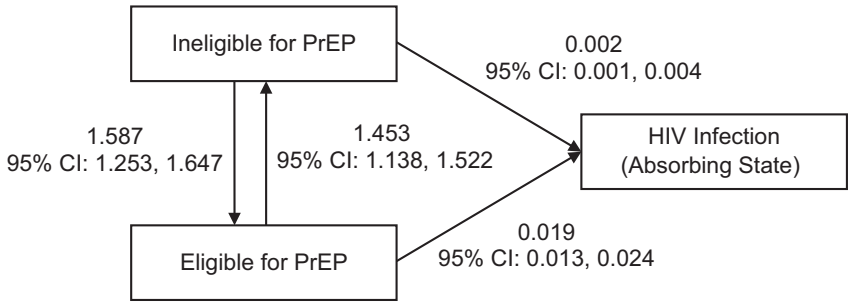

Figure 2. Estimated transition intensities and respective 95% confidence intervals (CIs) of the multistate model for the transition between preexposure-prophylaxis (PrEP) eligibility states and from these to human immunodeficiency virus (HIV) infection, Lisbon, Portugal, 2014–2020.

It is important to note that given the Markov assumption, on which the multistate models were based, future evolution depends only on the current state. This means that the estimated intensity transitions were independent of any previous states. Having this in mind, it is unequivocal that the risk of transition to an HIV-infection state was much higher when it was from the eligible-for-PrEP state. In practical terms, this means that once an individual meets any of the eligibility criteria for PrEP, he is at higher risk of becoming infected with HIV. The challenge is how to anticipate or detect these changes in a timely manner that allows preventive action. Transitions between eligibility states were similar, indicating that it was almost as likely for an individual to go from eligible to ineligible as to go from ineligible to eligible. The results of transition probabilities went in the same direction by showing that at any time point, the probability of transition between these 2 states was similar. However, it is important to note that this assumption greatly simplifies the dependence structure and may not be realistic. A semi-Markov model could be an alternative because it assumes that future state transitions depend also on time since entry in the present state. However, given that 44% of the participants only had 2 visits and 75% had 4 visits or fewer, the sequence of subsequent visits was not long enough to use that model.

These results showed that having an indication for PrEP based on behavioral information was likely to change over time and, most importantly, highlighted that those who were classified as ineligible at any point need to be reassessed for eligibility in a short time frame. This was previously discussed by Parsons et al. (17) in their proposal of a motivational PrEP cascade, in which individuals going in and out of risk would enter the cascade during times when PrEP was indicated. For individuals to be able to start and stop PrEP use, health-care providers need to be aware that when a person does not have a behavioral indication for PrEP at a given time point, there is only a short time frame to their lower risk. Therefore, individuals need to be advised accordingly and be given tools enabling them to self-identify a potential change in their behavior that leads to greater HIV

Table 5. Estimated Probabilities for Transition Between Preexposure Prophylaxis Eligibility States at Multiple Time Points, Lisbon, Portugal, 2014–2020

Time Point	Transition (Current State to State at Time Point)							
	Ineligible to Eligible		Eligible to Ineligible		Ineligible to HIV Infection		Eligible to HIV Infection	
	Probability	95% CI	Probability	95% CI	Probability	95% CI	Probability	95% CI
No. of days								
30	0.120	0.103, 0.138	0.109	0.094, 0.125	0.000	0.000, 0.002	0.002	0.001, 0.003
90	0.285	0.252, 0.319	0.258	0.228, 0.287	0.001	0.001, 0.008	0.004	0.003, 0.007
180	0.413	0.382, 0.443	0.373	0.343, 0.400	0.003	0.002, 0.013	0.008	0.005, 0.013
No. of years								
1	0.498	0.474, 0.515	0.450	0.428, 0.469	0.008	0.006, 0.024	0.014	0.009, 0.024
1.5	0.512	0.490, 0.528	0.463	0.443, 0.481	0.014	0.009, 0.031	0.019	0.013, 0.033
2	0.513	0.491, 0.531	0.463	0.443, 0.480	0.019	0.013, 0.046	0.025	0.017, 0.045

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

risk, know where to seek counseling or prevention, and have access to the prevention tools appropriate to their risk management preferences and needs. Expanding the criteria for PrEP by explicitly including 1) psychosocial components, interpersonal or dyadic, or other population-level factors, 2) the anticipation of risk, or 3) the discretion of prescribers in indicating PrEP for individuals not meeting eligibility criteria but perceived as being in need of PrEP can prevent missed opportunities to put individuals on a prevention track (18–20).

Considering the growing evidence that PrEP users are not lifetime users (21–26), these results call attention to the changes in indication for PrEP. Some studies showed that factors associated with PrEP discontinuation included changes in sexual behavior and HIV risk perception, adverse effects, adherence problems, and structural barriers to accessing PrEP (21–25). It is, therefore, increasingly important to focus on discussing the appropriate and sustainable preventive health paths to an individual's needs, which could include PrEP only at certain times (27).

It is important to note that our results are in the context of the absence of PrEP. Future investigations should consider PrEP as 1 additional state. In a 4-state model (ineligible, eligible, taking PrEP, and HIV infection), we would anticipate that eligible individuals would transition to the taking-PrEP state more often than from the ineligible state, and that transition from taking PrEP to HIV infection would be close to zero. Transitions between PrEP eligibility states and from these to HIV infection would likely remain similar to what was observed in our study. Alternative models could be theorized, but our 3-state model would not be appropriate in a context of PrEP availability. In cohorts like ours that are based in community-based HIV voluntary counseling and testing centers in countries where PrEP is being provided only by the national health service, this analysis may be difficult to pursue given that a reduction in participation from PrEP users is expected. This is because they are likely to be engaged in care at their PrEP provider and offered HIV testing as part of their PrEP monitoring.

A major strength of this study was the approach to measure state changes in PrEP eligibility and HIV infection, providing a novel assessment tool for risk prediction considering a longitudinal perspective. However, the limitations of our study need to be discussed. First, the limited number of transitions to HIV infection resulted in imprecise estimates, particularly of the ratio between the E–HIV and I–HIV transitions and transition probabilities to HIV infection. Though improbable, we cannot completely rule out chance as an explanation for the findings. Second, our structured questionnaire was not explicitly designed to measure PrEP eligibility. Because of that, the social vulnerability criterion was not assessed, and behaviors referred to the previous 12 months or the time in between evaluations rather than the 6-month period stated in the Portuguese National Health Service guidelines. Also, we may have missed more specific clinical information, such as contraindications to PrEP, leading to an overestimation of eligibility in our study. The peer-based approach provided by CheckpointLX may have partially mitigated bias due to social desirability and improved the accuracy of recall. Nevertheless, we could not exclude the possibility that those types of bias led to an underestimation of eligibility for PrEP, nor could we exclude that additional unmeasured sources of measurement error biased our results. Third, given that this was a cohort recruited at a community-based HIV voluntary counseling and testing center, these results are not generalizable to the entire MSM population. Participants in the cohort were more often self-identified as gay, better educated, and more aware of HIV risk, as they had been tested for HIV more frequently in the past (14), than those included in previous studies among MSM in Portugal conducted in different settings (28–31). Fourth, results may be biased due to loss to follow-up or suboptimal participation, as more than 50% of participants had only 3 visits. There were small absolute differences in terms of age and country of birth between those with and without a follow-up visit. However, the proportion of participants eligible for PrEP at baseline and assessed by each criterion was similar, as was the prevalence of a previous HIV test and the distribution of reasons for testing. Based on those measured proxies for sources of selection bias, it seemed unlikely that the findings from our complete case analysis were biased to an extent that would compromise our conclusions. However, those proxies were imperfect, and we cannot exclude that unmeasured sources of selection bias may have caused differences between our current findings and those that would have been observed had information from an unbiased sample of our source population been available.

In conclusion, among MSM attending a community-based HIV voluntary counseling and testing center in Lisbon, the transition intensities between being or not being eligible for PrEP were similar, but the probability increased with time, up to slightly more than 50%, showing that an indication for PrEP is likely to change over time. Our results also showed that reassessment of PrEP eligibility is needed even after an individual is classified as being ineligible at a given time point. Under these nonexperimental conditions, in 2 years, the probability of transitioning to HIV infection grew closer to the probability for those identified as eligible at the same initial point in time. Additionally, once an individual meets any of the eligibility criteria for PrEP, he is at higher risk of seroconversion. To anticipate and avoid changes to an eligible state is challenging and demands delivering PrEP sooner rather than later.

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