

Time to PrEP Uptake for Youth at Risk for HIV in the ATN CARES Study

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Introduction

Human immunodeficiency virus (HIV) is a primary sexually transmitted disease that if untreated can lead to acquired immunodeficiency disease (AIDS) and subsequent opportunistic infections. As of May 2021, there are 1.2 million people living with HIV in the United States alone.[1] The HIV epidemic in the U.S. has slowed slightly in recent years, but tens of thousands become infected with HIV every year. In 2019, 36,801 new HIV infections were reported by the CDC. This statistic highlights the need for continued efforts to improve HIV prevention practices

Pre-exposure prophylaxis (PrEP) is a drug that can significantly reduce the risk of getting HIV from sex or from injection drug use. PrEP is very effective and the CDC estimates that PrEP reduces the risk of infection from sex by 99% and from injection drug use by 75%. [2] Therefore, PrEP is highly recommended to those who are at high risk of HIV infection.

Significant efforts have been made to encourage those who are at high risk of HIV infection to start taking and keep taking PrEP. A common outcome to assess potential interventions is the usage of PrEP over time. Especially important is the time to first usage of PrEP for those who have not used it before. This is because the earlier a person starts using PrEP, the less likely that person is to become infected with HIV. This analysis will assess factors related to the time to PrEP uptake for the HIV- cohort who have not previously used PrEP.

Methods

The ATN CARES study[3] is multi-site randomized controlled trial in Los Angeles and New Orleans designed to assess community-based strategies for preventing and treating HIV in at-risk and HIV+ youth ages 12-24. The intervention in question is 4 arm stepped mHealth-based program to encourage good HIV prevention behavior. Every participant receives automated messaging (AMMI) to encourage good HIV prevention behaviors. The other arms additionally introduce peer support (PS), coaching, or both. The four intervention arms are therefore AMMI, AMMI+Coaching, AMMI+PS, and AMMI+PS+Coaching.

Over a period of 18 months, 1487 participants were recruited from Los Angeles and New Orleans-based gay-identified community centers and homeless shelters. The participants were followed for 24 months with data up to 12 months being available at the time of this analysis. Participants were scheduled for follow-up visits every 4 months, but in practice the time between visits can vary significantly. Participants were randomized into one of four intervention arms and filled out a survey with questions on sexual behavior, drug use, sexually transmitted infection diagnoses, demographics, and PrEP use. At each subsequent visit, the participants filled out a similar survey to track changes in these variables over time.

To select participants for this analysis, the participants were asked at baseline if they had ever used PrEP. Those who responded yes to this question were removed from the analysis. For the remaining participants, their responses to questions in the 4-month, 8-month, and 12-month surveys were used to determine time to PrEP uptake. Specifically, if a participant answered yes to the question “Have you used PrEP in the last 4 months?” at a follow-up visit, then the time of first PrEP usage was defined as the date of the visit. The time to PrEP uptake was calculated as the difference in weeks between the baseline

survey and time of first PrEP use. Participants who never started using PrEP or were lost to follow-up were considered right censored at their last visit.

Variables were selected based on prior knowledge of risk factors related to usage of PrEP. Demographic variables were also included. The variables include: city (Los Angeles or New Orleans), race (white, black, latino, other), sex, gender (cis-gender, transgender/gender-diverse), sexual orientation (gay, bisexual, heterosexual, other), age, insurance status (insured, uninsured/unsure), education (below high school, complete high school, some higher ed.), previous STI diagnosis (self-report), condomless anal sex in the past year, drug use excluding marijuana, number of sex partners (0-1, 2+), and homelessness in the past 4 months. All the variables are self-reported and are measured at baseline, even though follow-up data for some variables was available.

Statistical analysis

A Kaplan-Meier estimate of the probability of no PrEP uptake was constructed using the entire sample and plotted with a pointwise 95% confidence interval. Kaplan-Meier estimates of the probability of no PrEP uptake were constructed for each risk factor and demographic variable. Log rank tests were used to evaluate possible differences in survival among the levels of the predictor variables. The test were run once with equal observation weights and once with Peto-Peto weights which given more weight to earlier observations. The justification for using Peto-Peto weights is that it is better to start PrEP earlier because there will be fewer chances for HIV infection. The Kaplan-Meier curves were plotted with 95% pointwise confidence intervals and with the corresponding equal weight log rank p-value. Kaplan-Meier curves were also constructed and plotted for the intervention arms by the other predictor variables in order to assess the relative effect of the intervention arms.

Single predictor Cox PH models were fit to assess possible relationships with PrEP uptake. Estimated hazard ratios and p-values can be found in table 3. To address possible imbalances in risk factors and demographics, a χ^2 test of independence was conducted for each variable across the 4 study arms. In the case of age, an overall ANOVA F-test was used to determine if there was a significant difference in age across the intervention arms. Variables which were significantly associated with PrEP uptake or were unbalanced across arms were selected to be in a Cox proportional hazards regression along with intervention arm. After fitting the model, the proportional hazards assumption was checked for each of the variables in the model using tests of the normality of the Schoenfeld residuals and with graphical methods. For all Cox models, ties were handled using Efron's method and single variable Wald tests were used to assess significance of predictors.

Statistical analysis was preformed using R (4.1.0) in RStudio (1.3.1093). Packages used include survival (3.2.11), tidyverse (1.3.1), survMisc (0.5.5), table1 (1.4.2), and survminer (0.4.9). Unless otherwise noted, all tests were conducted with significance level $\alpha = 0.05$.

Results

Out of the 1487 HIV- participants in the ATN CARES study, 1294 (87%) had not used PrEP by the time of the baseline measurement. Baseline characteristics for these participants are reported in Table 1. Note that although participants were randomized to intervention arms, the χ^2 tests of independence reveal possible imbalances in many demographic variables and also for the risk factors condomless anal sex and recent homelessness.

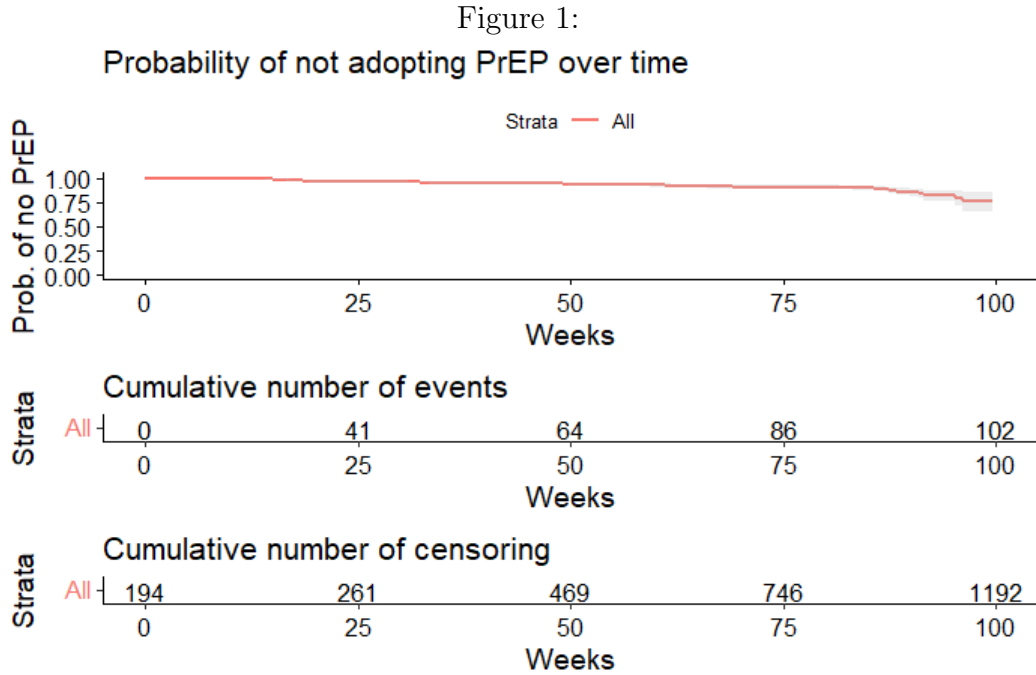
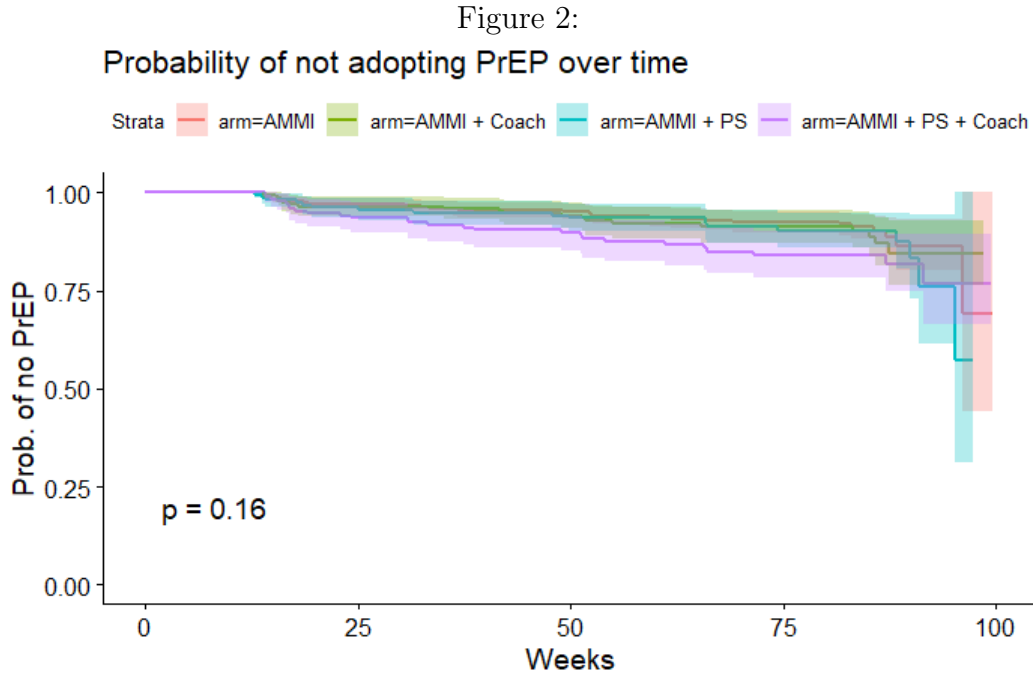


Figure 1 shows the Kaplan-Meier curve for the entire sample along with information on the cumulative number of events and censoring. Only 102 (8%) of the participants started using PrEP with 41 new users in the first 25 weeks and roughly 20 new users per 25 weeks after the initial period. Note that the number of events is small compared to the number of censored in the same time period, most of which are being lost to follow-up.

Figures in Appendix 1 show the Kaplan-Meier curves for each variable with corresponding log-rank p-value. Table 3 summarizes the log-rank p-values for the equal and Peto-Peto weights for the same variables. The curves and tests show that the probability of PrEP uptake differs between sex, gender, sexual orientation, education, and recent homelessness. Note that there was not a significant difference between intervention arms although Figure 2 shows a higher probability of PrEP uptake for the AMMI+PS+Coach arm early on. There was not a significant difference in p-values between the equal weighting and the Peto-Peto weights for the log rank tests. Figures in Appendix 2 show the difference in PrEP uptake between different study arms for each level of demographic and risk factor variables. These plots suggest possible subpopulations where there is a difference in PrEP uptake between the survival arms. For example, the plot by gender suggests a much bigger intervention effect in the transgender/gender diverse sample compared with the cis-gender sample.

The results from the single predictor Cox models can be found in Table 4. Study arm, sex, gender, sexual orientation, education, and homelessness were significantly associated time to PrEP uptake. These variables were included in the final Cox model along with the variables which had been identified earlier as having a possible imbalances across intervention arms. The final model included study arm, race, sex, gender, sexual orientation, education, condomless anal sex, and recent homelessness. Estimated hazard ratios with 95% confidence intervals are presented in Table 2.

In the full Cox model, sex, gender, sexual orientation, and recent homelessness were significant predictors of PrEP uptake. Females were less likely to adopt PrEP during the



study than males (HR: 0.36, 95% CI:0.158-0.83). Heterosexuals were less likely than gay participants to start using PrEP (HR: 0.15, 95% CI: 0.052-43). Participants who recently experienced homelessness were also less likely to have started PrEP (HR: 0.43, 95% CI: 0.227-0.83). Transgender and gender diverse participants were more likely to have started using PrEP during the study (HR: 2.72, 95% CI: 1.532-4.82). Note that there was no significant differences between the intervention arms when controlling for the other variables.

Appendix 3 shows the results for checking the proportional hazards assumption for the full model. Table 5 shows the results of testing the proportional hazards assumption for each variable in the full model. The proportional hazards assumptions seems to hold for all variables except for recent homelessness. A plot of the probability curves between homeless and non-homeless in Figure 3 also suggests a slight violation of the proportional hazards assumption. To address the possible violation, the variable $homeless * \ln(1+time)$ was added to the model. Table 6 shows the results of the new model. The new variable is significant but seems to introduce severe instability to the estimate of the coefficient for homelessness. Because the remaining coefficients do not significantly and change and because the violation of the proportional hazards assumptions seems to be minor, conclusions will drawn from the original model.

Discussion

The analysis suggests that PrEP uptake in ATN CARES study had more to do with demographic factors than with the study intervention. Unconditional on the other variables, there is some evidence of the AMMI+PS+Coach arm having earlier times to PrEP uptake, but the effect seems to disappear when conditioning on other variables. The significant variables in the full Cox model mostly reflect common knowledge about PrEP usage. Females and heterosexuals are at lower risk of HIV infection and thus may have less incentive and/or pressure from others to start using PrEP, resulting in lower uptake. Similarly, those who are or have recently experienced homelessness will be less

likely to start using a new medication, especially since proper use of PrEP requires daily use. Previous knowledge offers no explanation for why the transgender/gender diverse participants tend start using PrEP sooner. A subgroup analysis will be needed to find specific factors for these participants. Preliminary analysis suggests possible factors are age, previous STI diagnosis, and city.

This analysis has several limitations. By nature of the stepped intervention, it is not possible to estimate the effect of any specific intervention arm against not being in the study. The ATN CARES study sample does include those who used PrEP before the study, but because of censoring, there is no way to compare these individuals to those who were subject to possible intervention effects. For future studies, it would be beneficial to include a question about first time PrEP usage. Even though most participants would probably not remember the exact date, this would enable comparison with the pre-intervention PrEP users and also help to improve bias introduced by time of PrEP use being defined as the visit after the first usage occurred.

References

1. <https://www.cdc.gov/hiv/>
2. <https://www.cdc.gov/hiv/basics/prep.html>
3. <https://cch.ucla.edu/research/a-comprehensive-community-based-strategy-to-optimize-the-hiv-prevention-and-treatment-continuum-for-youth-at-hiv-risk-acutely-infected-and-with-established-hiv-infection-atn-cares/>
4. P. Grambsch and T. Therneau (1994), Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*, 81, 515-26.
5. Klein, J., and Moeschberger, M. (1997), *Survival Analysis—Techniques for Censored and Truncated Data*, New York., Springer

Table 1: sample characteristics

	AMMI (N=584)	AMMI + Coach (N=230)	AMMI + PS (N=253)	AMMI + PS + Coach (N=227)	P-value
City					
Los Angeles	314 (53.8%)	133 (57.8%)	134 (53.0%)	132 (58.1%)	0.488
New Orleans	270 (46.2%)	97 (42.2%)	119 (47.0%)	95 (41.9%)	
Race					
White	76 (13.0%)	31 (13.5%)	53 (20.9%)	40 (17.6%)	0.00838
African American	322 (55.1%)	105 (45.7%)	113 (44.7%)	100 (44.1%)	
Asian/HPI/NA/AN/other	45 (7.7%)	23 (10.0%)	19 (7.5%)	15 (6.6%)	
Latino	141 (24.1%)	71 (30.9%)	68 (26.9%)	72 (31.7%)	
Sex					
Male	438 (75.0%)	185 (80.4%)	211 (83.4%)	190 (83.7%)	0.00761
Female	146 (25.0%)	45 (19.6%)	42 (16.6%)	37 (16.3%)	
Gender					
Cis-gender	521 (89.2%)	184 (80.0%)	227 (89.7%)	200 (88.1%)	0.00162
Trans/GD	63 (10.8%)	46 (20.0%)	25 (9.9%)	26 (11.5%)	
Missing	0 (0%)	0 (0%)	1 (0.4%)	1 (0.4%)	
Sexual orientation					
Gay	170 (29.1%)	86 (37.4%)	116 (45.8%)	100 (44.1%)	<0.001
Bisexual	110 (18.8%)	60 (26.1%)	71 (28.1%)	69 (30.4%)	
Heterosexual	251 (43.0%)	55 (23.9%)	43 (17.0%)	40 (17.6%)	
Other	52 (8.9%)	29 (12.6%)	23 (9.1%)	18 (7.9%)	
Missing	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	
Age					
Mean (SD)	20.8 (2.11)	20.8 (2.11)	20.6 (2.28)	21.0 (2.20)	0.339
Median [Min, Max]	21.0 [14.0, 24.0]	21.0 [14.0, 24.0]	21.0 [14.0, 24.0]	21.0 [14.0, 24.0]	
Age category					
12-18	85 (14.6%)	38 (16.5%)	50 (19.8%)	35 (15.4%)	0.191
19-21	265 (45.4%)	104 (45.2%)	99 (39.1%)	86 (37.9%)	
22-24	234 (40.1%)	88 (38.3%)	104 (41.1%)	106 (46.7%)	
Insured					
Uninsured/Unsure	166 (28.4%)	64 (27.8%)	58 (22.9%)	69 (30.4%)	0.279
Insured	417 (71.4%)	166 (72.2%)	194 (76.7%)	157 (69.2%)	
Missing	1 (0.2%)	0 (0%)	1 (0.4%)	1 (0.4%)	
Education					
Below high school	161 (27.6%)	50 (21.7%)	70 (27.7%)	51 (22.5%)	0.266
High school diploma/equivalent	162 (27.7%)	65 (28.3%)	55 (21.7%)	59 (26.0%)	
Some/completed higher education	258 (44.2%)	114 (49.6%)	122 (48.2%)	110 (48.5%)	
Missing	3 (0.5%)	1 (0.4%)	6 (2.4%)	7 (3.1%)	
Previous STI					
No	391 (67.0%)	154 (67.0%)	175 (69.2%)	150 (66.1%)	0.834
Yes	192 (32.9%)	76 (33.0%)	75 (29.6%)	75 (33.0%)	
Missing	1 (0.2%)	0 (0%)	3 (1.2%)	2 (0.9%)	
Condomless anal sex in past year					
No	288 (49.3%)	101 (43.9%)	131 (51.8%)	88 (38.8%)	0.00777
Yes	291 (49.8%)	129 (56.1%)	118 (46.6%)	139 (61.2%)	
Missing	5 (0.9%)	0 (0%)	4 (1.6%)	0 (0%)	
Recent drug excluding marijuana					
No	348 (59.6%)	151 (65.7%)	156 (61.7%)	130 (57.3%)	0.33
Yes	236 (40.4%)	79 (34.3%)	97 (38.3%)	94 (41.4%)	
Missing	0 (0%)	0 (0%)	0 (0%)	3 (1.3%)	
Number of recent sex partners					
0-1	264 (45.2%)	105 (45.7%)	117 (46.2%)	98 (43.2%)	0.959
2+	309 (52.9%)	115 (50.0%)	136 (53.8%)	119 (52.4%)	
Missing	11 (1.9%)	10 (4.3%)	0 (0%)	10 (4.4%)	
Recent homelessness					
No	332 (56.8%)	160 (69.6%)	159 (62.8%)	150 (66.1%)	0.00172
Yes	243 (41.6%)	68 (29.6%)	80 (31.6%)	72 (31.7%)	
Missing	9 (1.5%)	2 (0.9%)	14 (5.5%)	5 (2.2%)	

Table 2: full Cox model

Characteristic	HR [†]	95% CI [†]	p-value
arm			
AMMI	—	—	
AMMI + Coach	0.84	0.48, 1.48	0.6
AMMI + PS	0.88	0.49, 1.56	0.7
AMMI + PS + Coach	1.23	0.73, 2.09	0.4
race			
White	—	—	
African American	1.56	0.84, 2.92	0.2
Asian/HPI/NA/AN/other	1.43	0.65, 3.14	0.4
Latino	1.18	0.62, 2.24	0.6
SEX			
Male	—	—	
Female	0.36	0.16, 0.83	0.016
gender			
Cis-gender	—	—	
Trans/GD	2.72	1.53, 4.82	<0.001
sexid			
Gay	—	—	
Bisexual	0.65	0.38, 1.09	0.10
Heterosexual	0.15	0.05, 0.43	<0.001
Other	0.64	0.31, 1.31	0.2
education			
Below high school	—	—	
High school diploma/equivalent	1.29	0.62, 2.71	0.5
Some/completed higher education	1.40	0.74, 2.64	0.3
Condomlessanalsex12m			
No	—	—	
Yes	0.92	0.60, 1.41	0.7
Homeless_RE			
No	—	—	
Yes	0.43	0.23, 0.83	0.011
[†] HR = Hazard Ratio, CI = Confidence Interval			

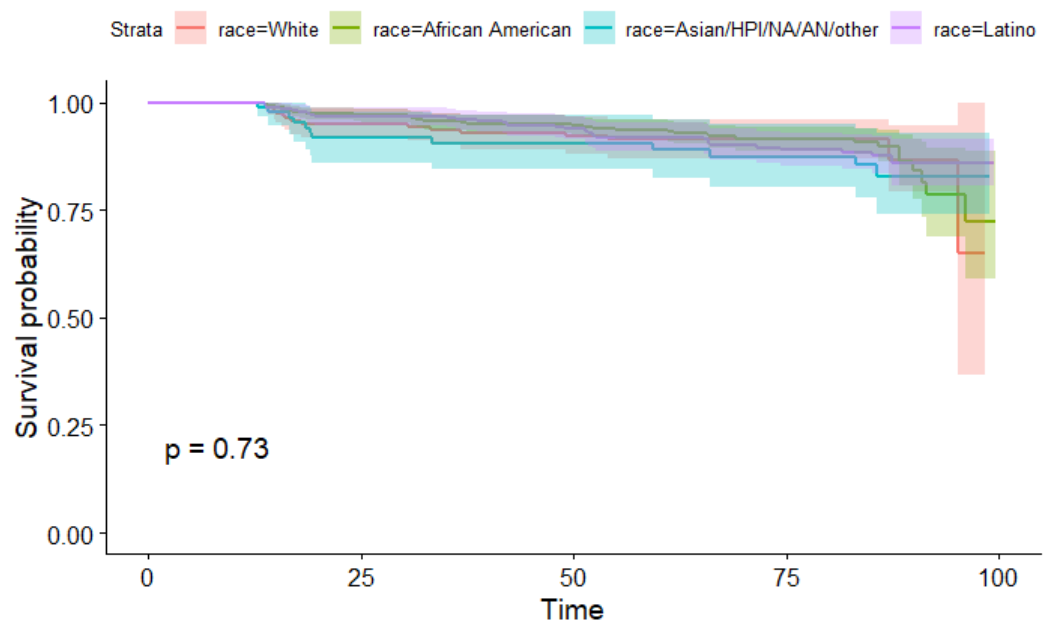
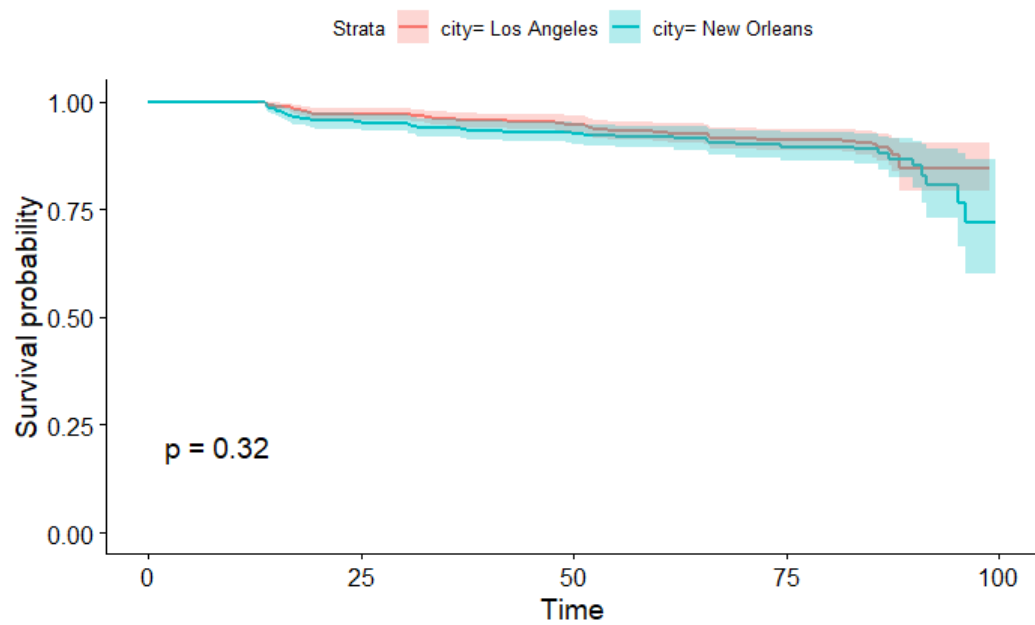
Table 3: log-rank tests

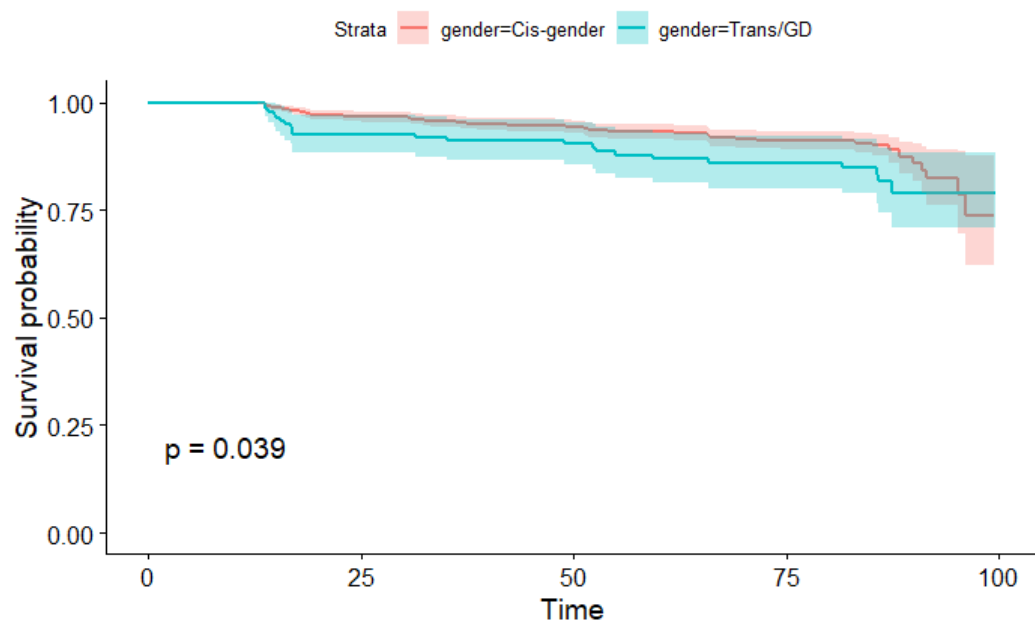
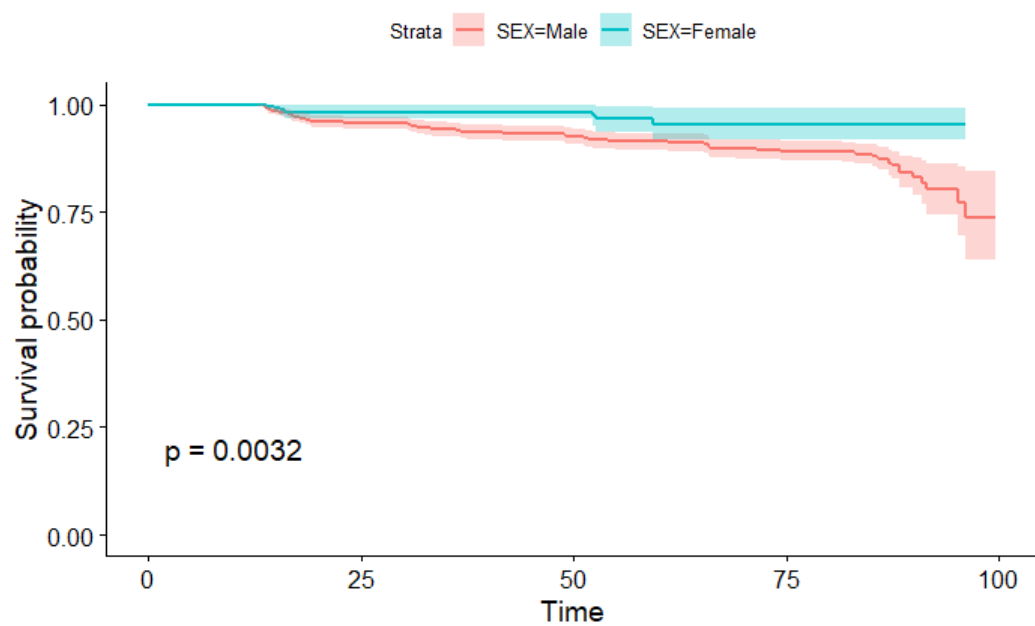
Variable	logrank	peto peto
Study arm	0.164	0.143
City	0.322	0.308
Race	0.730	0.686
Sex	0.003	0.003
Gender	0.039	0.032
Sexual orientation	<0.001	<0.001
Age	0.804	0.809
Insurance	0.091	0.096
Education	0.005	0.004
STI	0.461	0.443
Condomless anal sex	0.311	0.274
Drug use	0.445	0.447
# sex partners	0.133	0.128
Homelessness	<0.001	<0.001

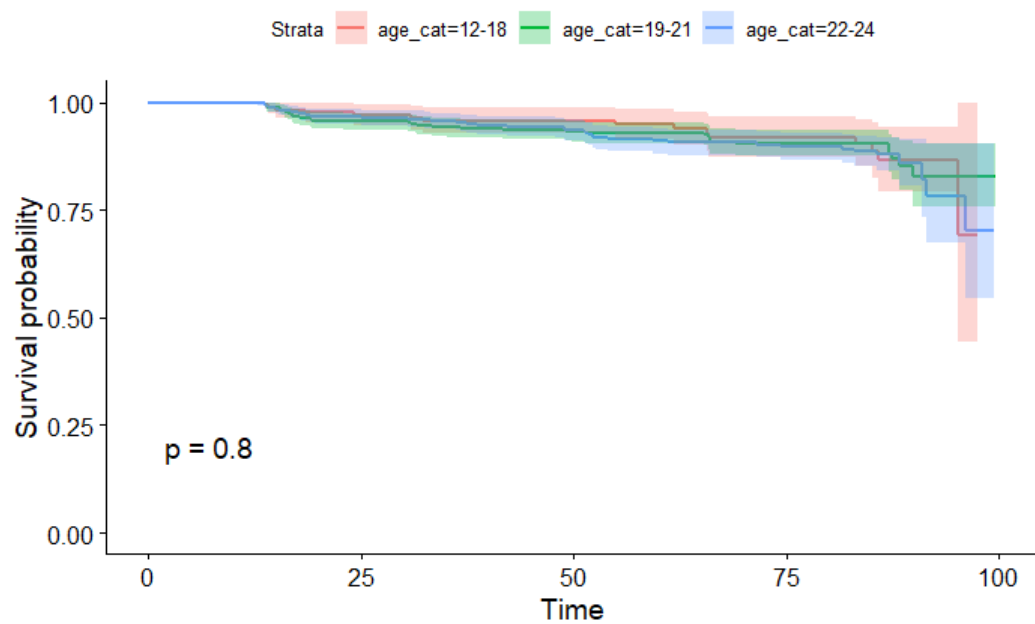
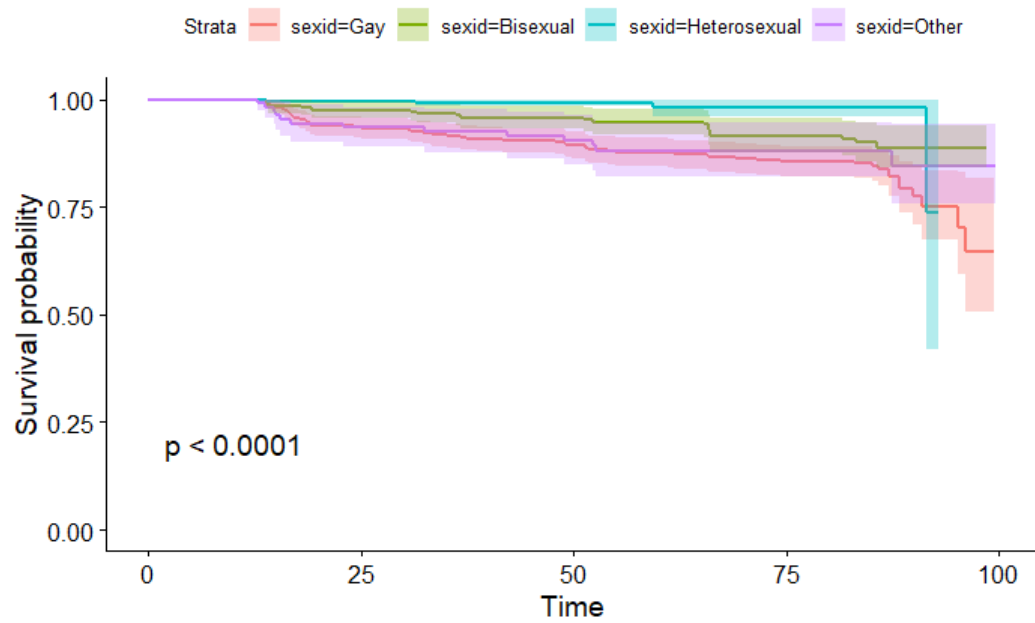
Table 4: univariate Cox regressions

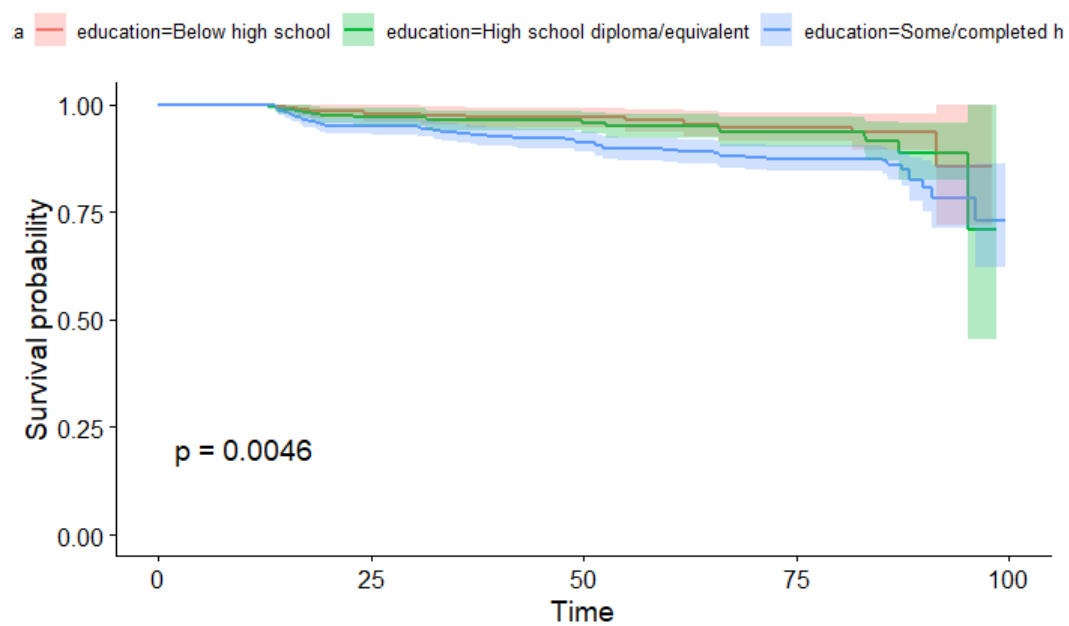
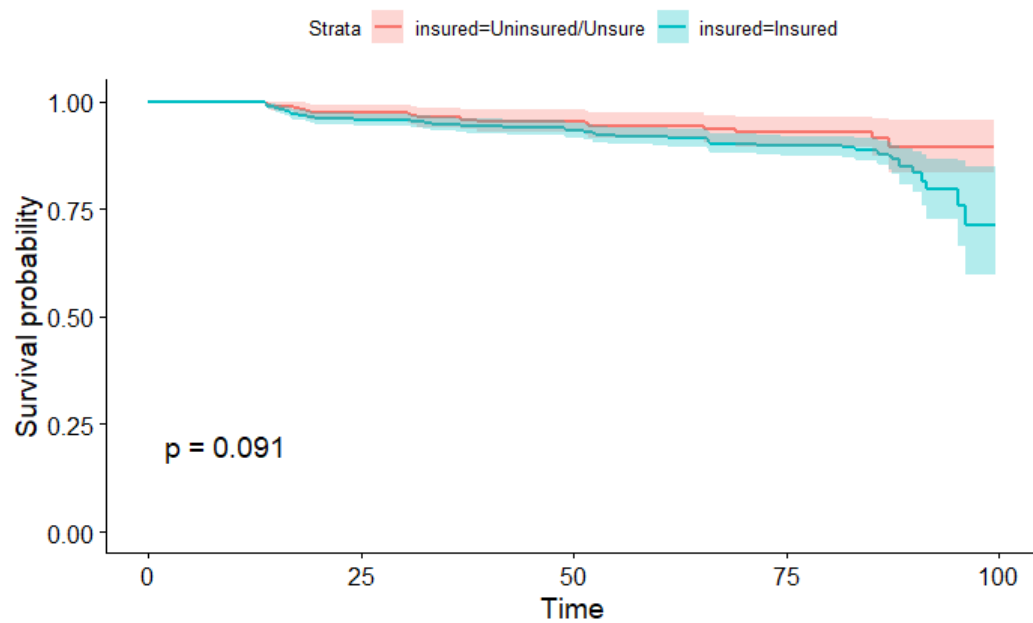
Variable	HR	p-value
<u>Study arm:</u>		
AMMI + Coach	1.16	0.61
AMMI + PS	1.22	0.47
AMMI + PS + Coach	1.77	0.03
<u>City:</u>		
New Orleans	1.22	0.32
<u>Race:</u>		
Black	0.91	0.75
Latino	1.02	0.94
Other	1.32	0.47
<u>Sex:</u>		
Female	0.33	0.001
<u>Gender:</u>		
Trans/GD	1.64	0.04
<u>Sexual orientation:</u>		
Bisexual	0.51	0.009
Heterosexual	0.11	< 0.001
Other	0.76	0.38
<u>Age</u>	1.05	0.25
<u>Insurance</u>	1.54	0.09
<u>Education:</u>		
Completed high school	1.35	0.42
Some/complete higher ed.	2.36	0.006
<u>STI diagnosis</u>	0.85	0.46
<u>Condomless anal sex</u>	1.23	0.31
<u>Drug use</u>	1.17	0.45
<u># Sex partners:</u>		
2+ partners	1.36	0.14
<u>Homelessness</u>	0.32	<0.001

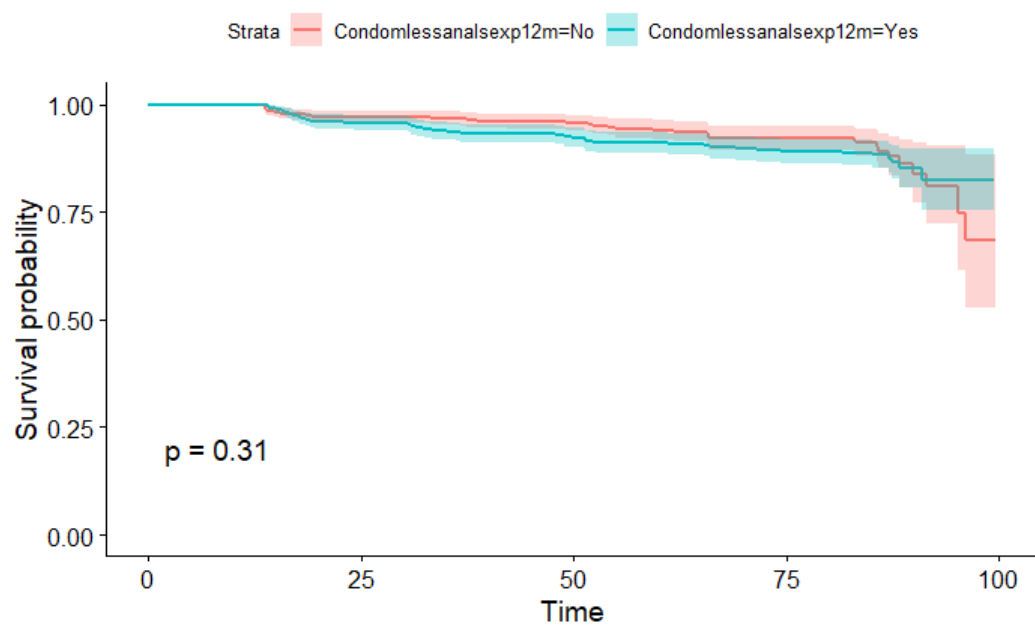
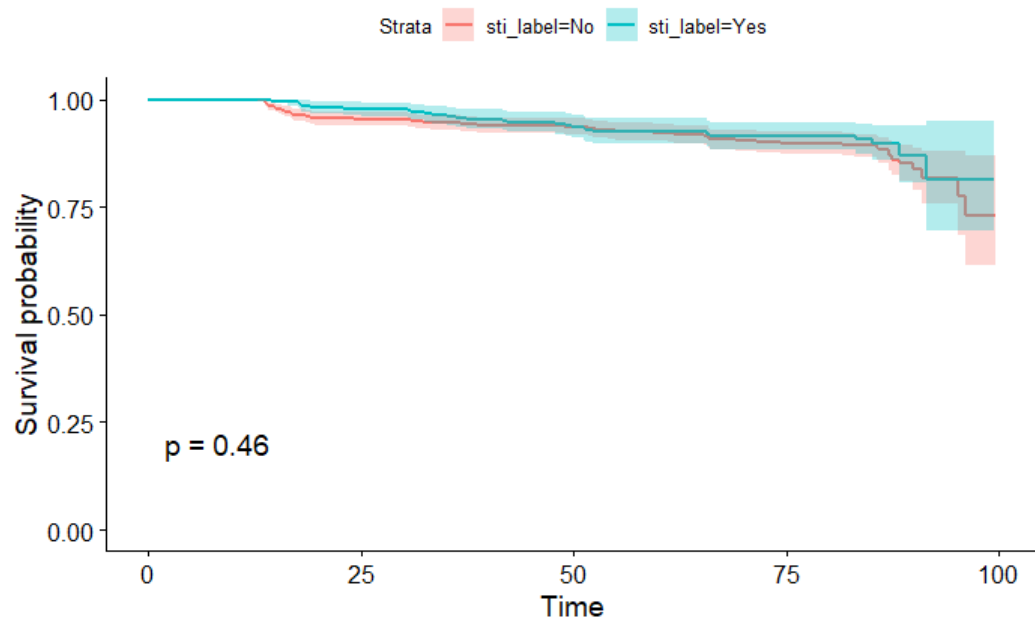
Appendix 1: Kaplan-Meier curves by risk factor

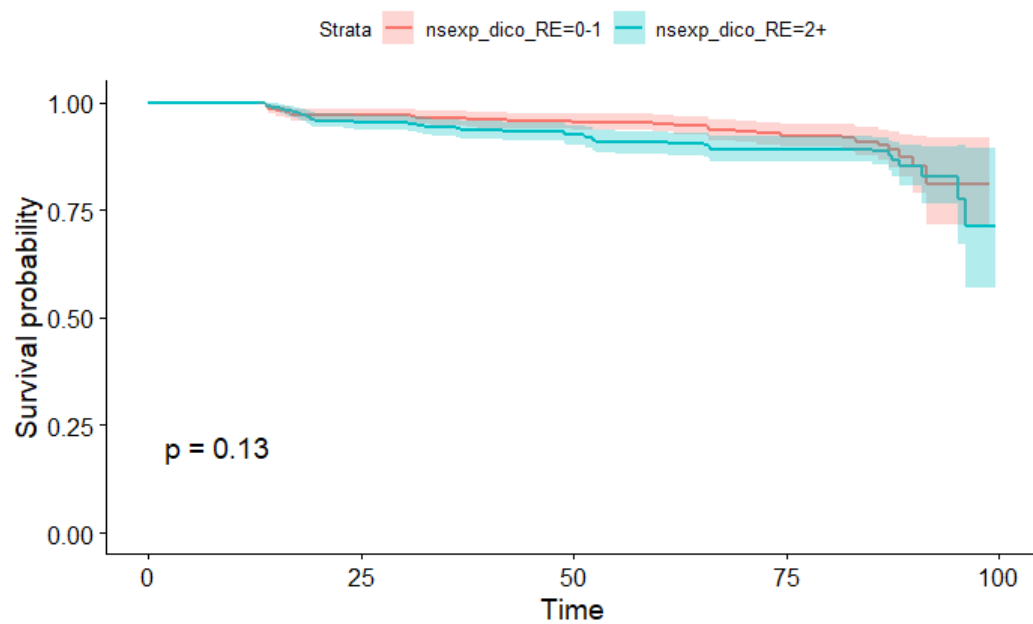
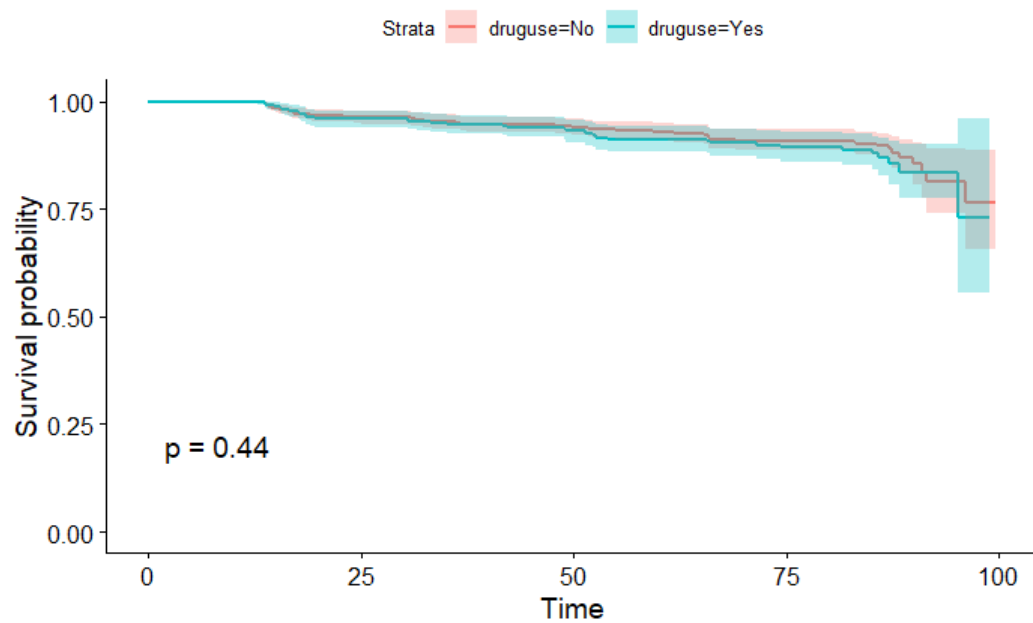


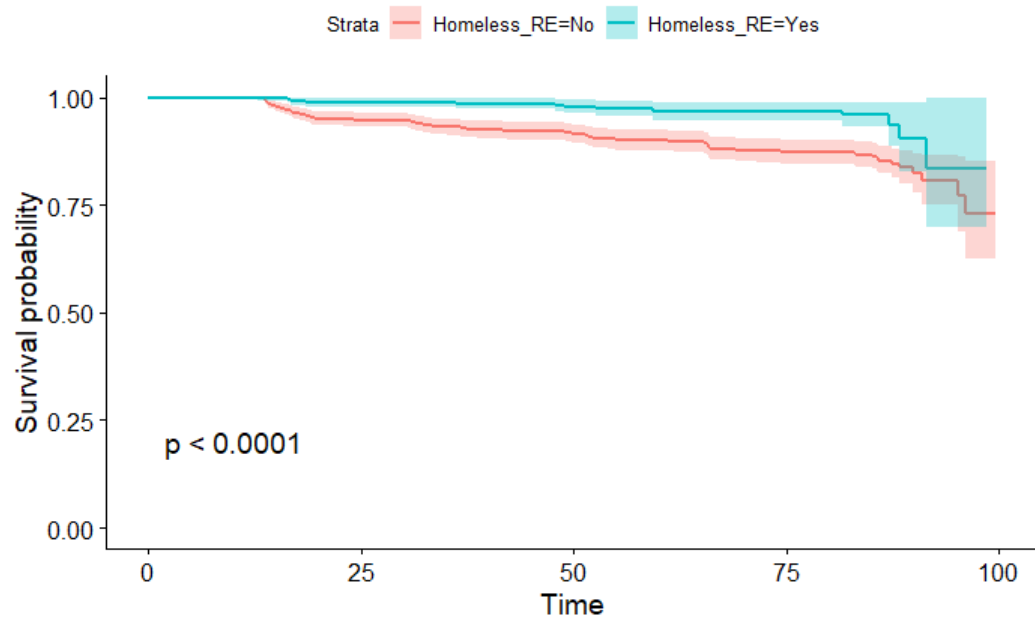




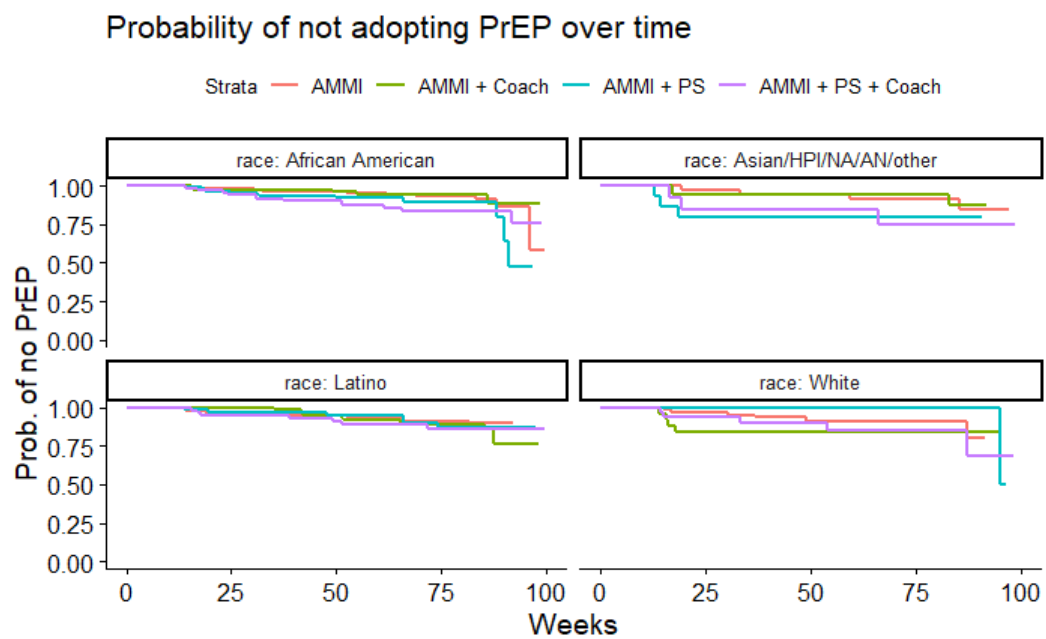
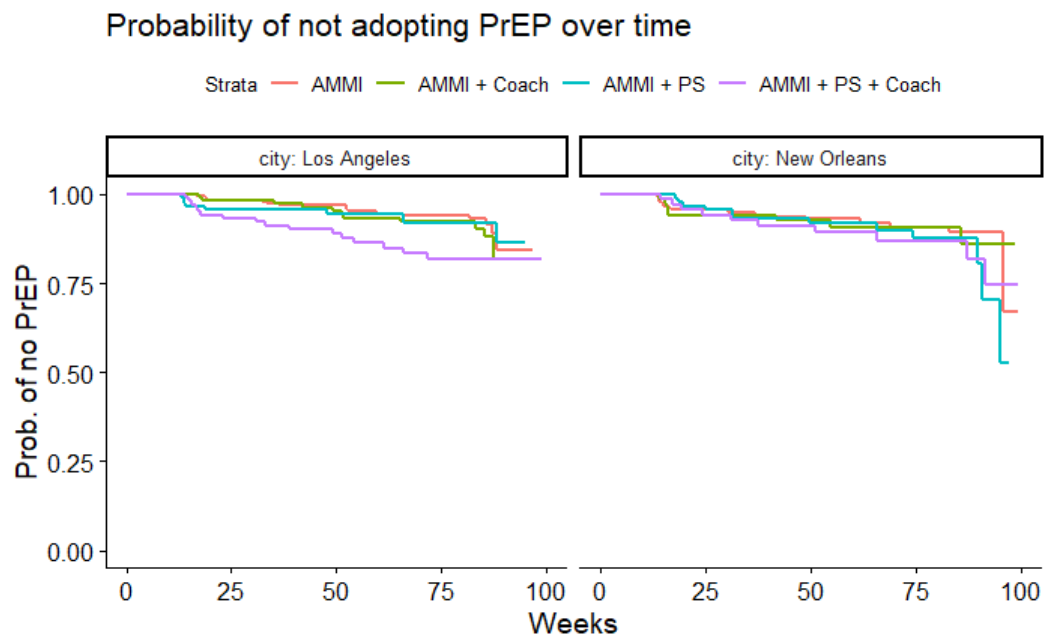




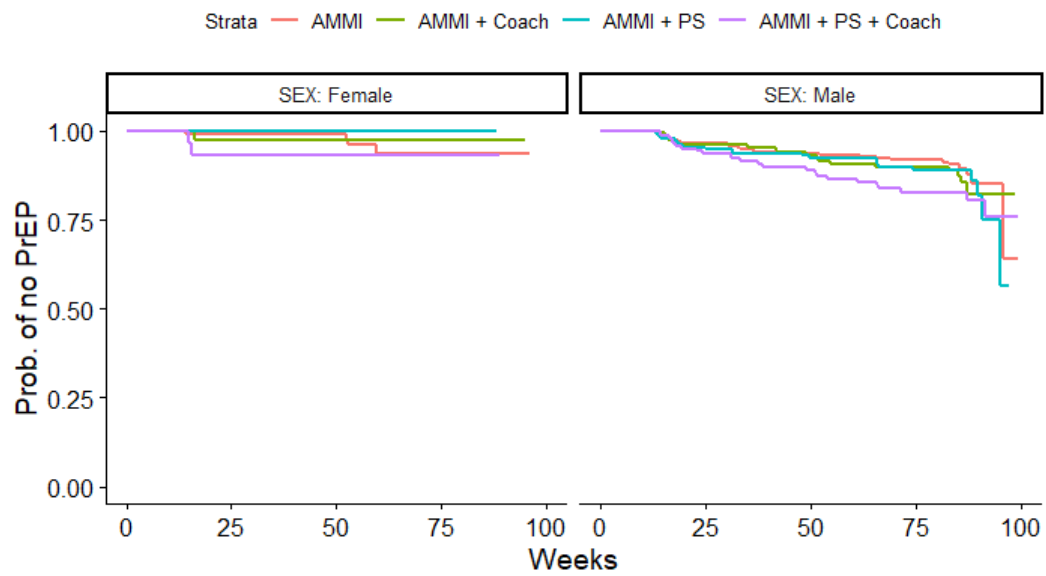




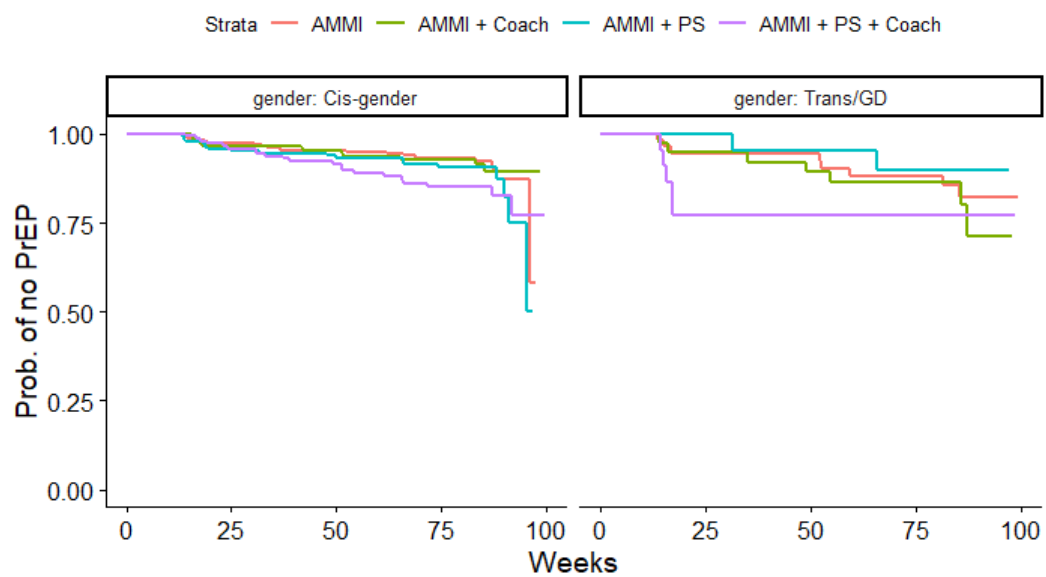
Appendix 2: Kaplan-Meier curves by arm by risk factor



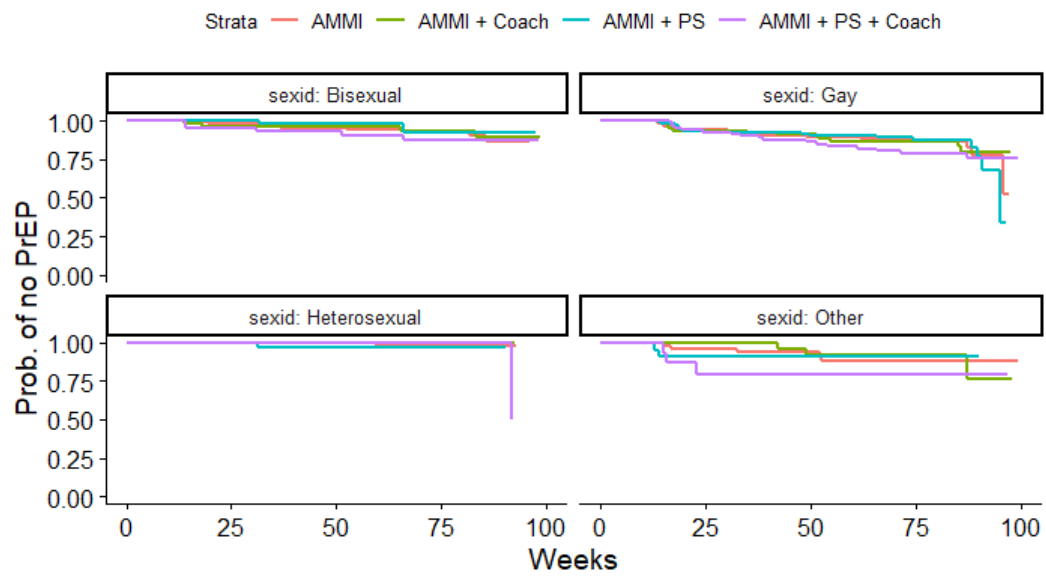
Probability of not adopting PrEP over time



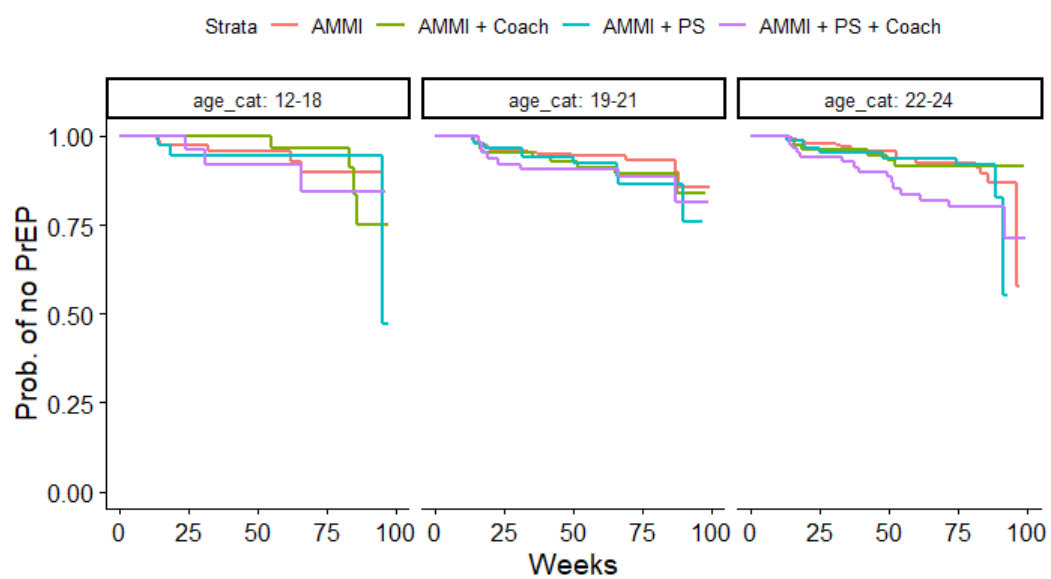
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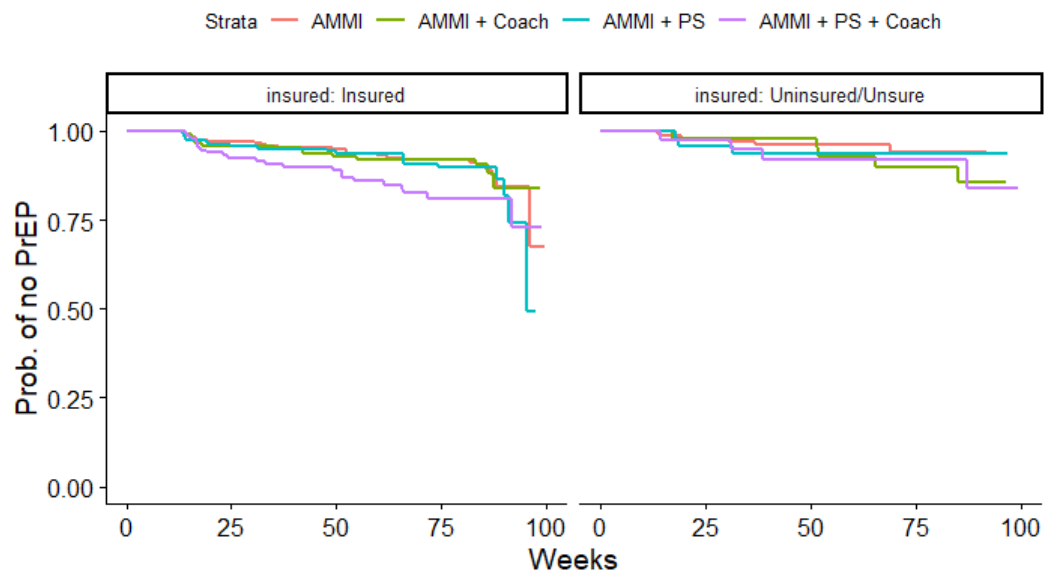
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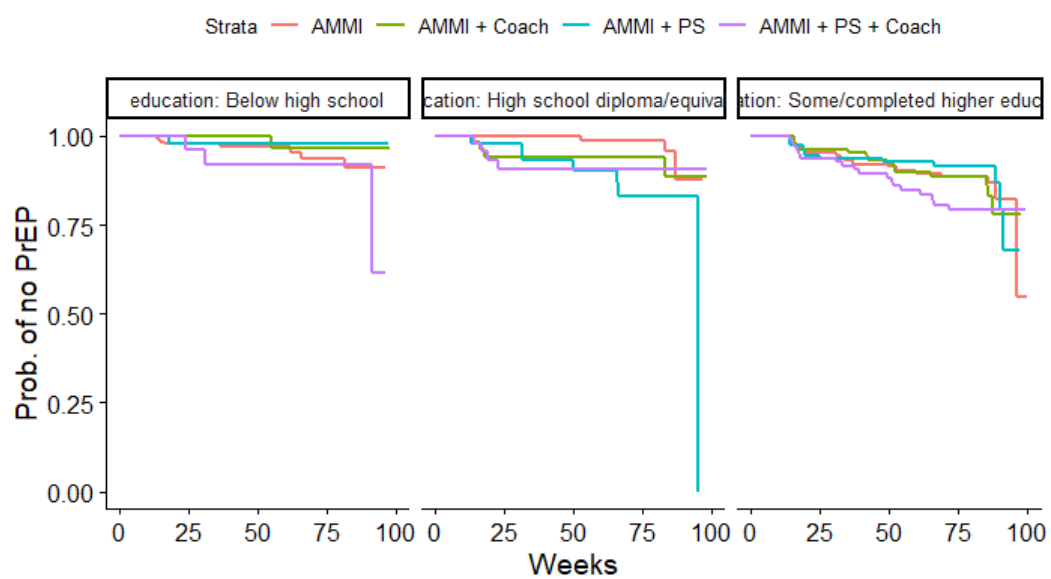
Probability of not adopting PrEP over time



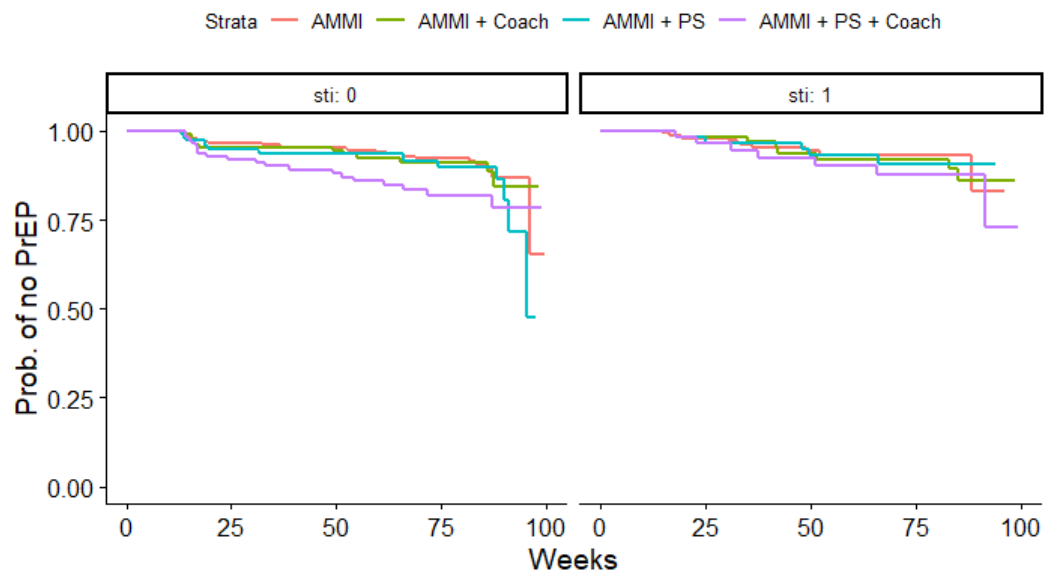
Probability of not adopting PrEP over time



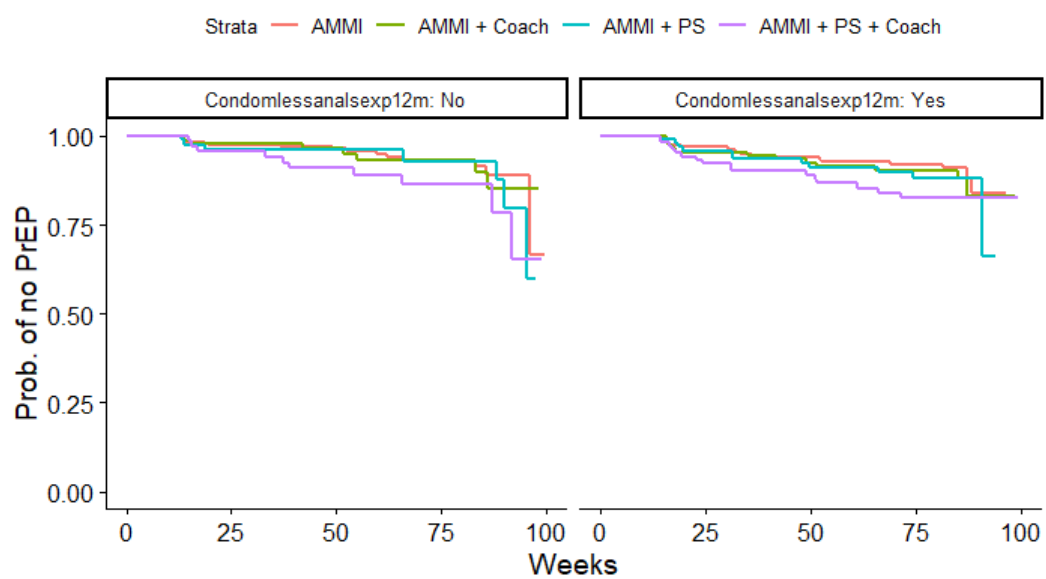
Probability of not adopting PrEP over time



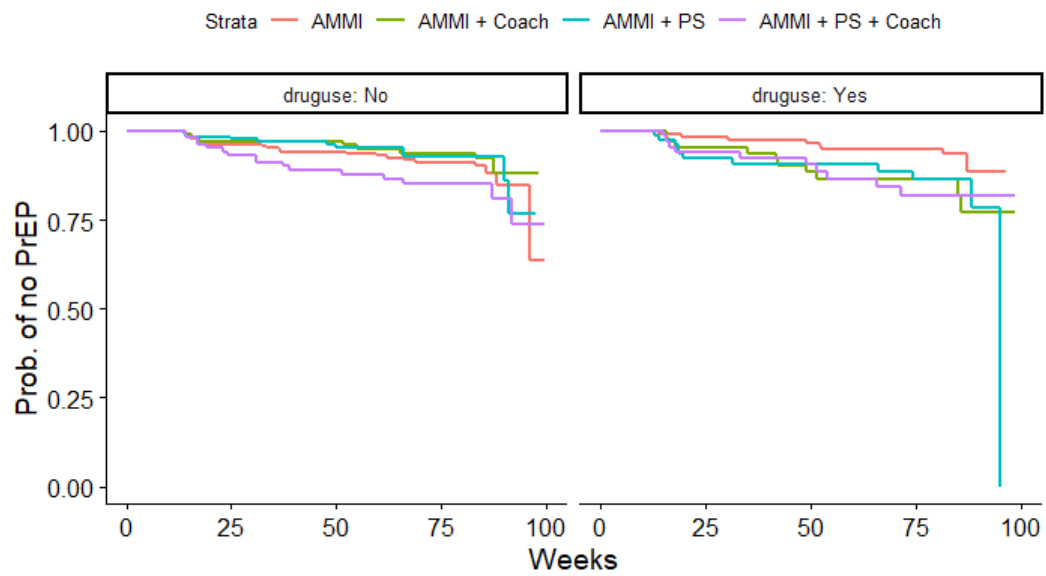
Probability of not adopting PrEP over time



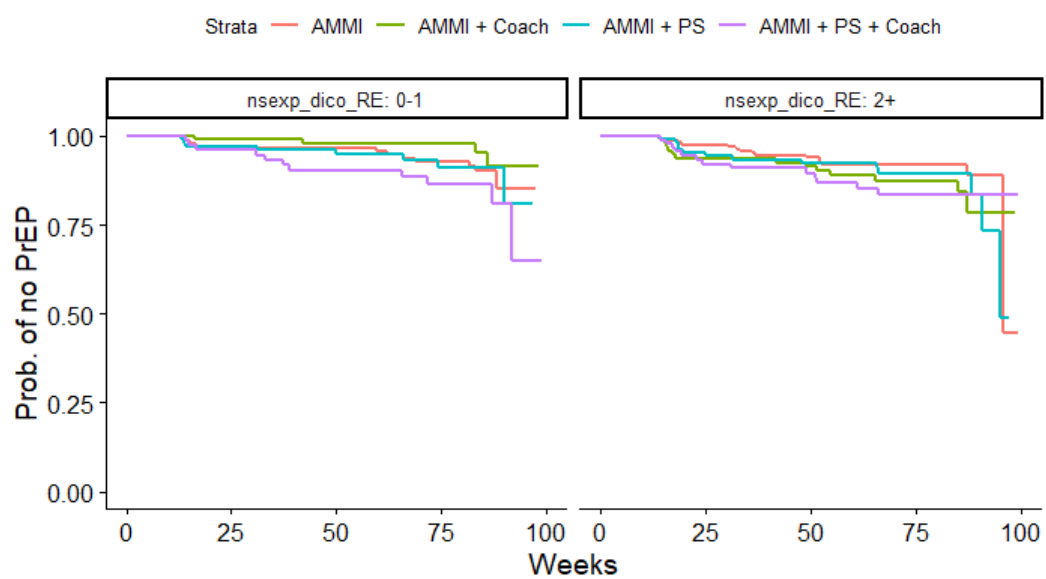
Probability of not adopting PrEP over time



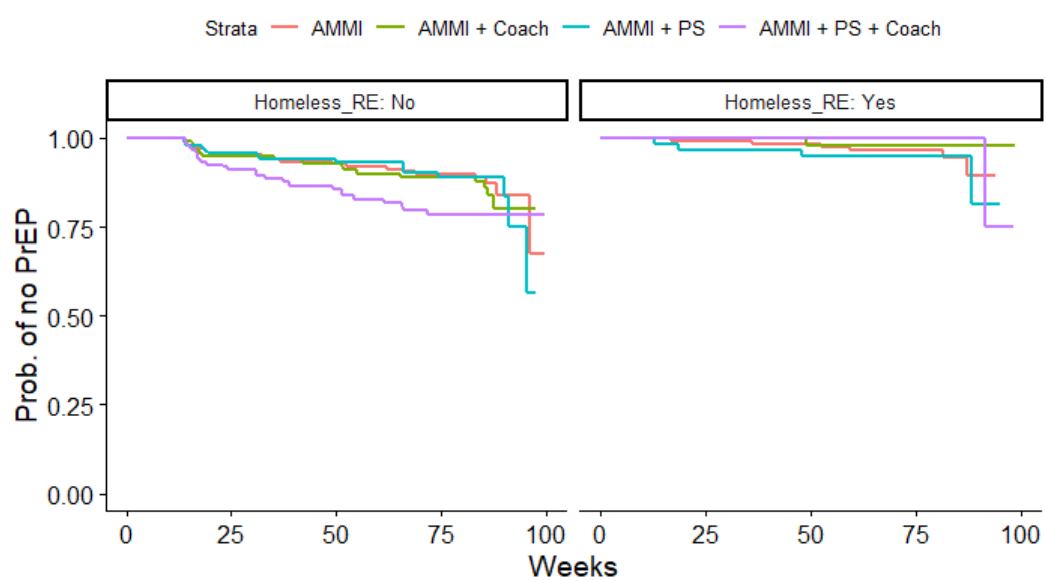
Probability of not adopting PrEP over time



Probability of not adopting PrEP over time



Probability of not adopting PrEP over time



Appendix 3: checking of proportional hazards assumptions

Table 5: tests of the PH assumptions for full model

Variable	χ^2	Degrees of freedom	p-value
Arm	2.29	3	0.51
Race	1.82	3	0.61
Sex	0.37	1	0.54
Gender	0.69	1	0.41
Sexual orientation	7.53	3	0.06
Education	0.84	2	0.66
Condomless anal sex	1.05	1	0.30
Homelessness_RE	4.11	1	0.04
Global	18.18	15	0.25

Figure 3:

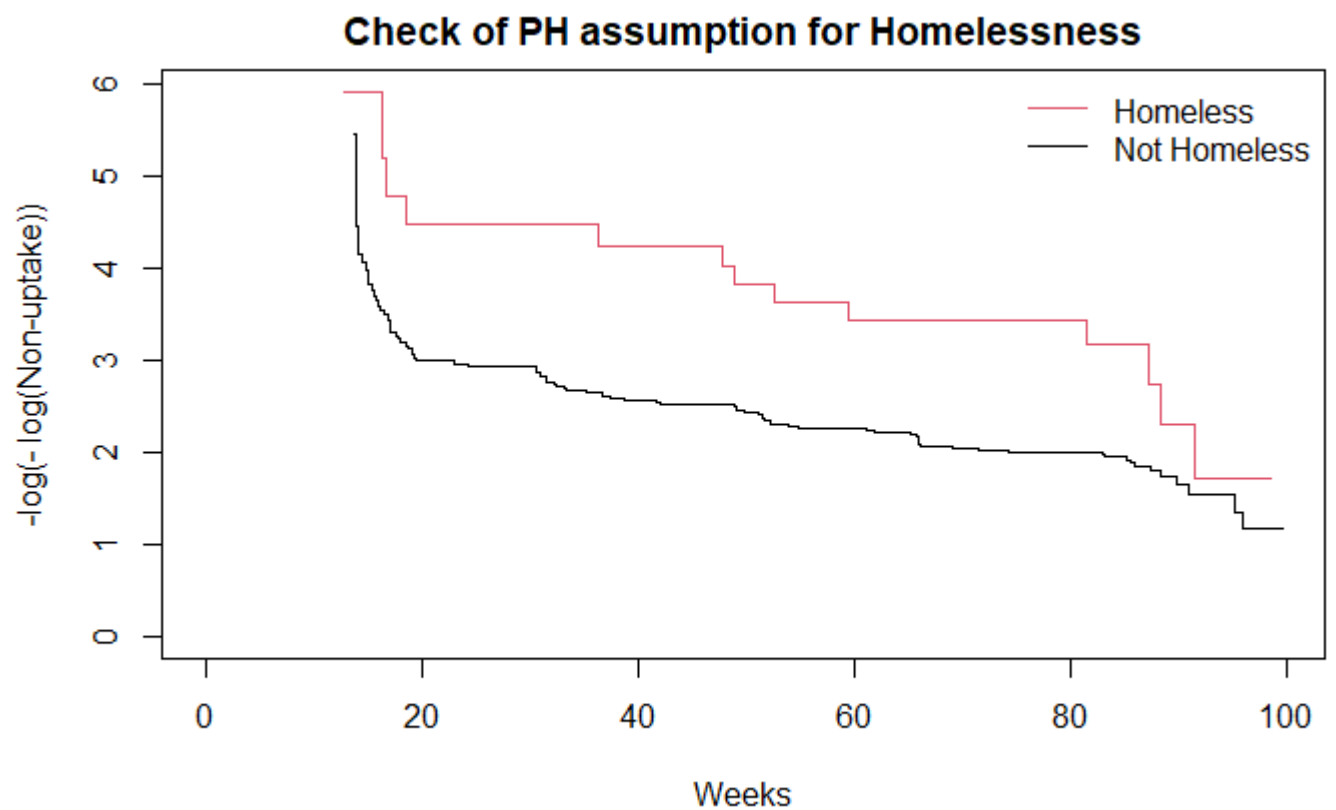


Table 6: Results of model with homelessness, time interaction

Characteristic	HR [†]	95% CI [†]	p-value
arm			
AMMI	—	—	
AMMI + Coach	0.84	0.48, 1.49	0.6
AMMI + PS	0.88	0.49, 1.56	0.7
AMMI + PS + Coach	1.19	0.70, 2.01	0.5
race			
White	—	—	
African American	1.61	0.86, 3.00	0.14
Asian/HPI/NA/AN/other	1.42	0.64, 3.13	0.4
Latino	1.25	0.66, 2.37	0.5
SEX			
Male	—	—	
Female	0.34	0.15, 0.77	0.010
gender			
Cis-gender	—	—	
Trans/GD	3.00	1.69, 5.34	<0.001
sexid			
Gay	—	—	
Bisexual	0.64	0.38, 1.08	0.094
Heterosexual	0.14	0.05, 0.40	<0.001
Other	0.61	0.29, 1.25	0.2
education			
Below high school	—	—	
High school diploma/equivalent	1.23	0.58, 2.58	0.6
Some/completed higher education	1.40	0.74, 2.65	0.3
Condomlessanalsex12m			
No	—	—	
Yes	0.93	0.61, 1.42	0.7
H1	1,781	44.2, 71,739	<0.001
H2	0.13	0.05, 0.34	<0.001
[†] HR = Hazard Ratio, CI = Confidence Interval			