# Aim 1: Describe the types of PrEP persistence trajectories among male PrEP users in the U.S. through cluster analysis.

## 2.1 Introduction

Men having sex with men (MSM) are the population most affected by HIV in the United States (U.S.). In 2018, MSM accounted for around 69% (n=2,6198) of incident HIV diagnoses in the US [1], despites only comprising about 2% of the U.S. population. Therefore, it is crucial to improve the effectiveness of HIV prevention strategies targeted toward MSM in order to reduce the overall burden of new HIV infections in the US, which has otherwise not been meaningfully reduced since 2014 [2].

Since the approval of TDF-FTC (tenofovir disoproxil fumarate /emtricitabine) by the Food Drug Administration in 2012, pre-exposure prophylaxis (PrEP) has been recommended for MSM at risk of HIV acquisition[3] due to its high efficacy in randomized controlled trials[4, 5]. Despite high efficacy in controlled settings, the effectiveness of PrEP is entirely dependent on user persistence over time. Based on findings from the open-label extension study of the iPrEX trial (a phase III PrEP trial among MSM), an adherence of at least 4 doses per week (or 57% of proportion of days covered in PrEP) is needed to achieve an optimal level of protection[6].

The lack of persistence in PrEP care over time posts a substantial challenge to its success as a HIV preventive measure among MSM. Data from PrEP clinics in three different cities indicated that 72% and 57% MSM users remained in PrEP care 3 months and 6 months after initiation, respectively[7, 8]. In addition, a multi-site review of clinical records suggests that only about 30% of PrEP-initiating MSM were retained at 12 months[9]. A follow-up survey of an open-label PrEP study at San Francisco and Miami found that only 40% of the respondents reported continual use of PrEP after the completion of the original study, even though 71% indicated very high interest in continuing with PrEP use after the study completion[10].

Although poor persistence in PrEP care within the first year of PrEP initiation has been well documented in the real world among MSM, few observational studies have analyzed persistence in PrEP care over a more extensive follow-up timeline. In addition, there have been various working definitions of PrEP persistence used in existing studies that analyze PrEP use over time (e.g., continued filling of PrEP prescription without a gap of >1 month at 3,6 and 12 months after initiation[11], having at least ¾ of 1 and 2 years with >50% of days in a month covered with PrEP supply[12], utilizing PrEP care in the last 6 month[13]). In many of these definitions, a person’s persistence in PrEP was determined by whether they met an arbitrary PrEP use threshold within a pre-specified, often broad, time intervals (e.g., 3 months, 12 months). It is often unclear how the implications of these definitions (for example, a person is “PrEP-persistent” at month 6 since initiation) are connected to the time-varying risk of suboptimal sero-protection, the understanding of which is vital to PrEP care case management. Furthermore, the broad time interval, in which PrEP persistence is determined, could increase the risk of ecological bias when it is used for inferring one’s PrEP use experience at more granular time points. As the result, there is a need to understand PrEP persistence by analyzing the longitudinal trajectory of PrEP use at a finer scale while considering the linkage between the dynamical patterns of PrEP use and their implication for the PrEP user’s sero-protection.

Furthermore, no existing studies to our knowledge have generated typologies of longitudinal PrEP persistence trajectories among the MSM populations in the U.S. From the perspective of PrEP care providers, it is important to leverage existing data to describe a typology of the longitudinal PrEP persistence trajectories because heterogeneity in PrEP use patterns among MSM may require tailored PrEP persistence support strategies. More specifically, such an understanding may inform clinicians about patterns of PrEP cessations and re-initiation, thereby aiding PrEP persistence interventions to target these key timings. In addition, an appropriately characterized typology of PrEP persistence patterns may facilitate patient segmentation, which in turn allows more efficient allocation of PrEP persistence intervention resources.

Thus, the overarching goal of this analysis is to describe the common patterns of longitudinal PrEP persistence using data-driven methodologies to identify latent clusters of PrEP persistence. We hypothesize that there is substantial heterogeneity in the longitudinal PrEP use behaviors such that we may qualitatively differentiate the mined patterns of PrEP persistence. Coy and Siegler found that age, health insurance characteristics and pharmacy type are associated with greater PrEP persistence (i.e., having >50% of a month period with PrEP supply for over 18 months) in the first two years since initiation among adult PrEP users in the U.S. The disparity in PrEP use by race/ethnicity[14] and neighborhood-level factors (e.g., socioeconomic economic status[15], PrEP service density[16]) and PrEP use have also been documented in existing literature. Therefore, we also aim to identify key individual-level and neighborhood-level characteristics associated with identified PrEP persistence patterns.

Findings regarding the presence or absence of heterogeneity in patient characteristics by PrEP persistence pattern class will facilitate the hypothesis-generating process for future research that aims to understand mechanisms by which individual-level and neighborhood-level characteristics are associated with certain PrEP use patterns. The product of this analysis will enable development of adaptive PrEP persistence interventions by providing specific recommendations on the identification of groups at high risk for PrEP non-persistence (according to the PrEP persistence pattern) as the intervention target.

## 2.2 Methods

### 2.2.1 Source population

The target population in this study is the adult (aged 18 – 65 years) MSM PrEP users in the US. Our collaborators from a national commercial pharmacy have an unrestricted access to HIV anti-retroviral prescription records, starting from January 2016. To obtain a representative and verifiable dataset for the target population, we initially extracted 17,054 adult male users from the collaborating pharmacy who had at least two years of longitudinal PrEP prescription fill records by 1/1/2020 and were initiated on PrEP in 1/1/2017~1/1/2018. A HIV anti-retroviral prescription record was identified as the PrEP initiation record if it satisfied the following criteria:

1. Either of the following conditions:
   1. It is the earliest prescription record with 30-day supply of TDF-FTC monotherapy in 2017
   2. It is the earliest prescription record with <30-day supply of TDF-FTC monotherapy in 2017 that occurred prior to the earliest 30-day FTC/TDF monotherapy in 2017.
2. No prescription fill records of antiretroviral medications existed within 12 months prior to the identified PrEP initiation record (i.e., from 1/1/2016 to the date of identified PrEP initiation record in 2017).

The requirement of monotherapy excludes prescriptions that are required to include other antiretroviral medications to treat HIV. The PrEP initiation requirement of having FTC/TDF monotherapy with 30 days of supply in 2017 is intended to prevent HIV post-exposure prophylaxis prescription from being falsely identified as the PrEP initiation records.

After identifying the PrEP initiation records for each extracted individual, we extracted the prescription fill records associated with TDF-FTC monotherapy that occurred between the PrEP initiation date and the earliest of the three following dates: 1) the end date of the two-year follow-up period since the PrEP initiation date; 2) the earliest date of ART prescription records; 3) the proxy HIV diagnosis dates, if collected from the patient.

The advantage of using a national chain pharmacy’s administrative dataset is that the database captures detailed medication fill records that reflect PrEP use behaviors in the real world for an extensive user population across the US. (It had pharmacy locations in 49 states and 20 of the most populous cities as of 2019.). Furthermore, past studies have validated pharmacy refill data as an appropriate approach to evaluate medication adherence and persistence[17, 18]. On the other hand, an inherent limitation of the pharmacy administrative dataset is that sexual orientation is not collected by the pharmacy. As a result, we will not be able to further filter for MSM among the extracted male PrEP users. This may undermine the transportability of our analysis’ findings. However, such a limitation should not cause serious concerns for the relevance of our analysis, because it is estimated that majority of the PrEP-indicated population in the U.S. are MSM (71%)[19] and less than 1% of the heterosexual active adults reported PrEP use[20].

### 2.2.2 Pre-processing of PrEP prescription data

The main challenge of inferring PrEP adherence patterns from PrEP prescription data is that the prescription data cannot reflect the actual dosing of PrEP. Findings from a large online survey of MSM suggest that around 95% of the PrEP users follow daily dosing[21]. Therefore, in the base analysis, we assumed that each PrEP user would follow a daily dosing schedule starting from the date of a prescription refill, and would go for the next refill only when the existing medication supply were exhausted. Starting from each subject’s PrEP initiation date, we repeatedly computed the proportion of days covered by PrEP medication intake in a biweekly interval (Eq. 1), which roughly corresponded with the duration of PrEP cessation after which protection from HIV became poor[22], over time. For the rest of this manuscript, we referred to this metric as biweekly *proportions of moving coverage*, or *PMC*. Using weekly moving strides, we created a 4000×103 time series matrix of PMC (Table 2).

**Eq. 1:** where = index number for the two-week windows; = the number of days with PrEP intake.

**Table 2. Empty data matrix for proportion of days covered**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Subject ID | (Day 1 – 14) | (Day 8 – 21) | (Day 15 – 28) | … | (Day 715 – 728) |
| 1 |  |  |  | … |  |
| 2 |  |  |  | … |  |
| 3 |  |  |  | … |  |

Because we are ultimately interested in evaluating PrEP persistence by the presence or absence of sufficient sero-protection, the PMC time series were converted to the time series of PrEP sero-protection using the minimum effective adherence threshold (i.e., 4 pills per week) as a binary cutoff (1= PMC ≥ 57%; 0= PMC <57%).

### 2.2.3 Baseline covariates

In addition to prescription data, we extracted individual-level demographic, financial, and pharmacy utilization information from the commercial pharmacy database and the patients’ ZIP-3-level characteristics using the 2013-2017 US Census American Community Survey[23] (Table 1). Variables in Table 1 are selected based on data availability and observed associations with PrEP use and HIV treatment adherence [14-16, 24-30].

**Table 1.** Individual-level and neighborhood-level characteristics selected for the association analysis with PrEP use trajectory patterns.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable Name | Definition/Note | Variable Type | Level (if applicable) |
| **Individual-level characteristics** | | | |
| Age at PrEP initiation (yr) |  | Categorical | 1. 18 to 24 years 2. 25 to 29 years 3. 30 to 39 years 4. 40 to 49 years 5. 50+ years |
| Primary payer type | Source of payment used most frequently in the 2-year tracking period. If two sources of payments were received, the commercial or government insurance coverage will be prioritized over other copay assistance. | Categorical | 1. Commercial 2. Government (Medicaid, Medicare, Tricare/Veteran administration) 3. Cash/Other |
| Average copay per month (USD) | Average out-of-pocket payment per month over the duration PrEP medication was filled | Categorical | 1. $0 2. > $0 |
| Pharmacy type |  | Categorical | 1. Community-based specialty pharmacy 2. Traditional retail pharmacy |
| **ZIP-3-level characteristics**  **Source: US Census American Community Survey (2013-2017)** | | | |
| Concentrations of black populations |  | Continuous |  |
| Concentration of Latinx/Hispanic population |  | Continuous |  |
| Concentration of residents with Bachelor’s degree or higher |  | Continuous |  |
| Concentrations of residents under poverty threshold |  | Continuous |  |
| Concentrations of residents uninsured |  | Continuous |  |
| Density of PrEP provider[31] | Unit: per 100,000 people | Continuous |  |

### 2.2.4 Sampling for study population

Due to the limited computational capacity of our pharmacy collaborator, we further sampled 4,000 individuals from the source population of 17,054 clients. To maximize the distributional representativeness of the study population (n=4,000) compared to the source population, we iteratively implemented stratified sampling for 100 times based on the following covariates: 1) age at PrEP initiation; 2) average monthly copay; 3) primary payer type; 4) duration under sub-optimal PrEP sero-protection, derived from the binary PrEP sero-protection data matrix. Age at PrEP initiation, average monthly copay and primary payer type were selected because of their observed association with PrEP persistence in our previous study[12]. Duration under suboptimal PrEP sero-protection was computed to summarize the overall PrEP persistence in the two-year follow-up period.

The 100 sampled datasets were then ranked based on their closeness to the source dataset in regard to the bivariate distributions. Root-mean square error (RMSE) was used to assess an average distance in spearmans’ correlation coefficients among covariate pairs where both are continuous variables. For covariate pairs where at least one variable is categorical, RMSE on the cross-tabulation frequencies were selected as a distance measure, which were then averaged among all the categorical covariate pairs. The sample dataset with the best rank (weighted between continuous and categorical distance ranking) was selected as the study population, or the working dataset for the subsequent trajectory clustering analysis.

### 2.2.4 Group-base trajectory modeling (GBTM)

GBTM is an application of finite mixture modeling that has been widely used for identifying latent distinct clusters of individuals following similar trajectories (i.e., repeatedly measured phenomenon that progress over time)[32]. Under the finite mixture modeling framework, GBTM assumes that the observed trajectories arise from the realization of a finite mixture of pre-specified distributions. A mixture distribution is a probability distribution derived from an assembly of other random variables, in which a data value is realized from a component random variable that is randomly selected from that assembly of random variables. The distribution of trajectories (i.e., ), under the aforementioned framework, may be described by the following formula:

**Eq. 2:**

Where ) denotes the time series of measurements on individual *i* over the follow-up period; denotes the membership probability in group *j* (the finite mixture is composed of J groups or component random variables) for individual *i*; denotes the likelihood of conditioned on membership in group *j* and the corresponding distribution parameter vector .

To reduce model complexity, GBTM (as most finite mixture models that handle longitudinal data) assumes conditional independence between measurements at different time points (for example, and ) given their group membership [32], such that the conditional likelihood function of may be written as ). Trajectories will be modeled as a polynomial function of time. GBTM can also be used to model the effect of hypothesized risk factors on group membership (i.e., , where is risk factor vector for individual *i*) under the assumption that data trajectories are independent of risk factors given group membership.

In this analysis, the following cumulative probit model [33] was used to model the conditional distribution of PrEP sero-protection given group membership.

**Eq. 3:**

Where denotes whether a PrEP user *i* is considered sufficiently protected by PrEP over the next two weeks at week *t* since the initiation of PrEP given he belongs to group *j*; denotes the cumulative distribution function of a standard normal distribution; denotes the number of weeks since the PrEP initiation date and denotes the order of the group-specific polynomial used to model potentially non-linear trajectories.

### 2.2.4 Evaluation of PrEP trajectory cluster

A major challenge with any data mining analysis, including GBTM, is that there is no external data on ground-truth label that can be used for validating the detected cluster solution. Therefore, we assessed both the internal validity and cluster interpretability of the discovered PrEP trajectory clusters (or groups) solutions.

In an ideal world, we would evaluate all possible mined cluster structures given specified hyperparameters, which include the number of PrEP use trajectory clusters to mine (K) and the assignment of group-specific polynomial order in the time variable (e.g., if K=3, polynomial order for group 1,2 and 3 could be 2,2, and 3 respectively). However, the number of models evaluated would have increased substantially, which may not be feasible given limited computational power. Furthermore, the qualitative interpretability of the mined PrEP use trajectory cluster would likely decrease as K increases. To limit the number of evaluated models and maintaining cluster interpretability, we only assessed K=1~6. We used the 2rd polynomial order in the time variable for all K groups (the 3rd order of polynomial was not explored due to non-convergence and computational limitation of our collaborators).

#### 2.2.4.1 Internal validity

A cluster solution with good internal validity should maximize model fit while balancing model complexity (i.e., the greater the number of clusters to mine, the greater model complexity), and have a clear assignment of cluster membership. To assess model fit, we computed and compared the Bayesian information criterion (BIC). Lower BIC reflects greater data likelihood penalized for model complexity.

To assess the clarity of group assignment, we computed the average posterior probabilities of group membership for each discovered group by averaging the posterior probabilities of group membership among subjects assigned to the same group (according to the maximum probability of group membership). Higher average posterior probabilities of group membership indicate clearer partition. A K-group model with acceptable internal validity should have average posterior probabilities ≥ 0.70, and a close correspondence between the estimated probability of a group membership and the proportion of study subject assigned to that group [34-36].

In addition, clear group assignment may also be indicated by a large ratio comparing the odds of model-predicted group assignment against the odds of random group assignment (known as “Odds of Correct Classification” in the group-based trajectory modeling textbook by Nagin 2005[37]). An adequate K-group model should have “Odds of Correct Classification” ≥ 5 [36, 38, 39] for all discovered groups.

To ensure cluster representativity and avoid selecting an overfitted model, all cluster sizes for a selected model should at least account for 5% of the study population[40]. To assess the strength of evidence against the hypothesis of homogenous PrEP use trajectories, we approximated the Bayes factors (using the formula[41]:) comparing the selected K-group model against the single-group model. The obtained Bayes factor may be interpreted as the ratio of marginal likelihood of the selected model to that of the single-group (i.e., homogenous trajectory) model.

#### 2.2.4.2 Cluster interpretability

From a data mining perspective, the ultimate goal of cluster analysis is to find a grouping or label structure that can provide meaningful, clinically relevant insights, given the domain understanding, on the differences between detected clusters. To facilitate this qualitative evaluation of the discovered PrEP persistent patterns, the predicted trajectories of PrEP sero-protection over time by cluster membership were visualized. A group-specific predicted trajectory was interpreted as the time-varying probabilities of optimal PrEP sero-protection in the two-week window, along the follow-up time of a typical PrEP user belonging to a trajectory group. To better characterize each PrEP user cluster, the timings and duration of PrEP cessation in which the probabilities of PrEP sero-protection consistently hover around or below 30% (the cutoff is informed by examining the predicted trajectories in Sagaon-Teyssier et al 2018[40]) were described. We also identified timing of possible PrEP re-initiation, if any, along the follow-up period.

### 2.2.5 Association analyses

To assess possible heterogeneity in the baseline characteristics between PrEP users of different PrEP persistence patterns, we compared the descriptive statistics by the final cluster membership. We also assessed the associations between the PrEP use trajectory cluster membership and these characteristics. We aimed to identify the key correlates of PrEP persistence pattern, which may further inform the development of future research that explores the causal relationship between certain characteristics and PrEP persistence patterns.

Ideally, we would incorporate these characteristics as independent variables in the multinomial logistic function for predicting group membership in the GBTM (Eq. 2 & 6) to account for the uncertainty of fuzzy cluster membership in the association analysis.

**Eq. 6:**

Where *i* denotes subject index; *j* denotes the index for the mined clusters; denotes regression constant; denotes the coefficient of a characteristic variable; denotes the value of a characteristic variable for individual *i*; and are set to zero for identifiability[41].

Failure to do so may result in biased inference regarding the association between the mined PrEP use trajectory patterns and the baseline characteristics [41, 42]. However, because of the non-convergence issue in the model fitting process, we alternatively used unregularized and Lasso multinomial logistic models, in which we regressed the GBTM-predicted group membership (according to the maximum posterior probability of group membership) on the baseline characteristics. By shrinking regression coefficients toward zero[43], the Lasso regularization could be used to reduce multicollinearity in the model and encourage parsimonious selection of relevant correlates of the heterogenous PrEP persistence patterns and. The optimal magnitude of the regularization parameter was determined by the10-fold cross validation on multinomial deviance. To facilitate interpretability of the regularized regression coefficients across all trajectory groups, we adopted grouped lasso penalty on all predictor variables such that group-specific coefficients belonging to the same predictor variable are penalized the same.

### 2.2.6 Sensitivity analyses

We evaluated the impact of non-daily dosing schedules on the mined typology from the GBTM. First, we would like to define new terms:

* **PrEP assessment interval:** the time interval bounded by two consecutive PrEP prescription fill dates, or the end date of the two-year tracking period
* **Adherent PrEP consumption period:** the duration between the start date of a PrEP assessment interval and whichever comes earlier between the following two dates: 1) the end date of the PrEP assessment interval or 2) the end date of a 7-day extension period after the end of the prescription’s days supply. Given that most PrEP prescription fills contain 30-day supply, the 7-day relaxation corresponds to a dosing frequency of approximately 6 doses per week, which fits the working definition of daily dosing schedule referenced in a nationwide survey study measuring PrEP dosing frequencies [21]. The adherent PrEP consumption period effectively represents the approximal duration a PREP prescription fill would last if a PrEP user mostly maintain daily dosing frequency.

We assigned 10% of PrEP users to follow nondaily dosing regimen. Non-daily PrEP users were randomly selected from the subset of PrEP users who had at least one PrEP assessment intervals in which the interval lengths were greater than the length of the adherent PrEP consumption periods. To preserve analysis parsimony, we assumed that all PrEP users completed their prescribed supply before the next PrEP assessment interval. The aforementioned selection process gave us two subpopulations of study subjects:

1. **Daily PrEP users:** all of their PrEP assessment intervals would strictly follow daily dosing regimen, as in the base analysis assumption.
2. **Non-daily PrEP users**: they would strictly follow the daily dosing regimen for the PrEP assessment intervals in which the interval lengths were within the adherent PrEP consumption periods. However, they would use a non-daily PrEP regimen for the PrEP assessment intervals in which the interval lengths were greater than those of the adherent PrEP consumption periods. A nationwide survey study on PrEP dosing frequency suggested that large proportions of non-daily PrEP user followed an event-based PrEP dosing schedule (primarily on-demand 2-1-1 dosing regimen) or a regular schedule (e.g., every other day, on “T” [Tuesday, Thursday] and “S” [Saturday, Sunday]) [21]. Assuming MSM having roughly 1 sex per week as an average American adult[44], both event-based or regular non-daily dosing schedule would be equivalent to following a PrEP dosing regimen of 4 pills/week. For the PrEP assessment interval eligible for non-daily PrEP regimen, the dates of PrEP intake were randomly selected between the interval start date and the earlier of the two following dates: interval end date or the date prescription was expected to run out given the 4 pills/week dosing schedule. The total number of selected PrEP intake dates in a PrEP assessment interval should equal the prescription days supply of that interval.

A modified PMC and PrEP sero-protection time series matrices were created, following the selections of PrEP intake dates per non-daily dosing schedule. The binary PrEP sero-protection time series matrix was analyzed using the same GBTM procedures as in the base analysis. Given the limited computational availability of our collaborator, we only implemented one iteration and compare the resulting iteration-specific cluster structures (i.e., the number of discovered groups, the proportion of group membership, group-specific predicted trajectories) with that obtained in the base analysis.

## 2.3 Results

### 2.2.7 Strengths and limitations

One primary strength of our study is that we utilize the longitudinal PrEP prescription fill data to analyze PrEP persistence trajectories over time, which address the knowledge gap in the time-varying PrEP use habits that could not be observed in measures that summarize PrEP adherence in relatively extended time intervals. Furthermore, our study aims to provide straight forward, clinically friendly interpretation of the discovered PrEP persistence trajectory patterns that are linked to time-varying risk of suboptimal sero-protection from PrEP. In addition, we took advantage of the healthcare administrative data from a U.S. national pharmacy chain and formulate PrEP persistence trajectories based on daily dosing schedule. Such a study design will allow our analysis to complement on the findings from a similar study where Sagaon-Teyssier et al used GBTM to group the trajectories of PrEP adherence probabilities among French and Canadian MSM who follow event-based dosing schedule in a PrEP clinical trial (ANRS IPERGAY).

Our study is not without limitations. One primary limitation is that the collaborating pharmacy chain does not collect data on actual PrEP use from their customers (i.e., our study subjects). Although we attempt to address the impact of uncertainty around their actual PrEP use habits on trajectory clustering by simulating various common dosing schedules in our sensitivity analyses, the simulated datasets may or may not represent the study subjects’ true PrEP use experiences. Furthermore, the number of dataset simulations for assessing the impact of non-daily dosing schedules may be limited by our computational capacity.

In the sensitivity analysis, we attempt to address the possible misclassification bias of PrEP sero-protection for users who switched to a different pharmacy chain during their follow-up period by restricting the trajectory clustering analysis on study subjects who continue to fill non-PrEP medications after their last prescription fill of PrEP. However, there could be residual misclassification among PrEP users who frequently switch back and forth between two or more pharmacies. Despites this possibility, we deem that the proportion of such users exist in our study population is ignorable.

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