Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Kelsey C. Coy Date

Predictors of PrEP Adherence Over a Two-Year Period Among a National Sample of Patients in the United States, 2015-2017

By

Kelsey C. Coy
Master of Public Health

Epidemiology

_____

Aaron Siegler
Committee Chair

Predictors of PrEP Adherence Over a Two-Year Period Among a National Sample of Patients in the United States, 2015-2017

By

Kelsey C. Coy

B.S., Butler University, 2013

Thesis Committee Chair: Aaron Siegler, Ph.D., M.P.H.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Epidemiology
2018

Abstract

Predictors of PrEP Adherence Over a Two-Year Period Among a National Sample of Patients in the United States, 2015-2017
By Kelsey C. Coy

Introduction: Despite the efficacy of pre-exposure prophylaxis for HIV prevention (PrEP), there have been few quantitative studies to date studying PrEP adherence over a long period of time in real world settings. Using pharmacy refill data as a validated approach, the objective of this study was to use a sample of patients from a large national chain pharmacy to describe adherence to PrEP care over a two-year period, and to explore correlates with PrEP care adherence.
Methods: We analyzed the pharmacy fill records of 7,148 eligible individuals who initiated PrEP in 2015 at a large national chain pharmacy, considering a modified Proportion of Days Covered (PDC) in three time periods as the adherence outcome of interest. Individuals were followed for 24-months post-initiation to explore correlates with PrEP care adherence from initiation to 1 year, 1 to 2 years, and initiation to 2 years of follow up.
Results: Adherence rates were 63% from initiation to 1 year and 56% from 1 to 2 years, with 35% retained from initiation to year 2. The age category with the lowest adherence was 18-24, with 43% adherent from initiation to 1 year and 54% adherent from 1 to 2 years. Males had higher adherence than females with 34% of females retained from initiation to 1 year and 49% retained from 1 to 2 years. Individuals with commercial insurance and individuals who attended a local specialty pharmacy also had higher retention over time. All three models had the same predictors; being male, being older than 18-24 years, having an average monthly copay of $20 or less, having commercial insurance, and attending a local specialty pharmacy were significantly associated with adherence from initiation to 1 year, 1 to 2 years, and initiation to 2 years of follow up.
Conclusions: PrEP adherence was suboptimal from initiation to 1 year, 1 to 2 years, and initiation to 2 years of follow up due to a combination of demographic, financial, and pharmacy factors. Further research is needed to explore how social, structural, or individual factors may undermine or enhance adherence to PrEP and retention in PrEP care.

Predictors of PrEP Adherence Over a Two-Year Period Among a National Sample of Patients in the United States, 2015-2017

By

Kelsey C. Coy

B.S., Butler University, 2013

Thesis Committee Chair: Aaron Siegler, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2018

Contents

Predictors of PrEP Adherence Over a Two-Year Period Among a National Sample of Patients in the United States, 2015-2017

Background

Pre-exposure prophylaxis for HIV (PrEP) is a safe and highly effective strategy to protect against HIV acquisition, with clinical trials demonstrating that drug levels consistent with daily use result in over 99% reduction in HIV transmission (1-8). PrEP with daily oral use of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) is still relatively new to the clinical setting; the US Food and Drug Administration approved this combination for HIV prevention in 2012, and the Centers for Disease Control and Prevention published clinical practice guidelines in 2014 and updated in 2017, with interim guidelines first published in 2011 (9).

Protective effects of PrEP require dosing adherence and treatment persistence; in two clinical trials where PrEP efficacy was not demonstrated, poor adherence was the primary contributing factor (1, 10-13). In one study of PrEP users, higher adherence was associated with being over age 25, while being uninsured was associated with low adherence over the 30 days prior to the survey (14). These predictors, age >25 and having commercial insurance, are also associated with medication adherence outside of PrEP (9, 10, 14, 15). Clinical trials and other studies have found higher PrEP adherence in male participants compared to females; one study found that men had an OR of 2.0 compared to women (95% CI: 1.5-2.7) of <80% PrEP adherence, determined by pill count (16). Another study found no association with gender and adherence, but found that female gender was associated with discontinuation of PrEP (RR 2.6; 95% CI: 1.5-4.6) (17). Additionally, the only clinical trials that did not demonstrate PrEP efficacy due to low adherence were among women only (12, 13).

There have been few quantitative studies to date studying PrEP adherence over a long period of time. In one study of men who have sex with men (MSM) in three U.S. cities over six

months, 72% were retained in care at three months and 57% were retained in care at six months; insurance status and medication costs were not found to be significant barriers to retention (15). High adherence, defined as taking at least four pills in the previous week, was achieved by 92% at both three and six months had adherence greater than 4 or more pills per week in the previous week (15). A survey of MSM recruited from online social networks who use PrEP found that 92% reported daily dosing in the last month, and that being older than 18-25 years old (ORs range from 2.54-5.64 for older age groups) was significantly associated with perfect adherence, while insurance status was not (14). Another study followed up with MSM who had completed the 36- to 48-week US PrEP Demonstration Project four to six months prior and found that 39.9% had taken PrEP since the study's completion, with cost and lack of insurance as the greatest perceived barriers to accessing PrEP (16).

Pharmacy refill data has been validated as an approach to assess antiretroviral therapy medication adherence (18), and allows for assessment of adherence among large groups of persons taking a medication in pharmacy settings. One study examining PrEP adherence measurement in the iPrEx trial compared self-reported adherence through interviews, self-report through CASI surveys, adherence estimated by pill count, and adherence calculated by the Medication Possession Ration (MPR) to drug detection levels of TDF-FTC and found that MPR outperformed all other measures (19). Other studies have similarly found MPR as a valuable measurement tool for ART adherence assessment, and that it is well correlated with patient-level health outcomes (20, 21); additionally, this type of information can be extremely useful to detect non-adherence or gaps in treatment (22). Common measures of adherence for pharmacy-refill data include MPR and Proportion of Days Covered (PDC) (23-25). MPR, defined as the summation of the days' supply of medication refills across an interval, has been more commonly used in previous research. PDC, defined as the ratio of the number of days covered by the prescription fills and the number of days between the first fill and the end of the measurement

period, is recommended by the Pharmacy Quality Alliance for adherence measurement. The objective of this study is to use a sample of pharmacy refill data from a large national chain pharmacy to describe adherence to PrEP care over a two-year period, and to explore correlates with PrEP care adherence at one- and two-years follow-up.

Methods

We analyzed the pharmacy fill records of individuals who had at least a 60-day supply of TDF-FTC for PrEP during 2015. Data are from a large national chain pharmacy and consist of a simple random sample that constitutes a substantial proportion of individuals prescribed TDF-FTC for PrEP in the overall pharmacy dataset. Individuals eligible for the analysis were aged at least 18 years and had filled at least a 60-day supply of TDF-FTC in 2015. Individuals initiating therapy prior to 2015 or who had filled other antiretroviral medication prescriptions used to treat HIV were not eligible for the analysis. For each individual eligible for the analysis, data were collected for a 24-month time period following each individual's PrEP treatment initiation.

Deidentified data for 7,148 individuals eligible included demographic variables (age category and gender), financial variables (average copay per month and payer type), geographic variables (driving distance in miles from patient's home address to nearest store and urban/rural status of pharmacy), and pharmacy type. Driving distance was calculated using road distance in ArcGIS from the patient's home address to the nearest pharmacy. Urban/rural status was categorized as urban, less dense urban, suburban, and rural according to the population density of the pharmacy location used most frequently for each individual. Payer was defined as commercial, government, or cash/other, assigned based on the primary payer that was used by the patient most often in the study period. The cash/other category includes cash, manufacturer's coupons, other, and unknown sources. Monthly copay was calculated as the average copay per month per patient over the time that they were in PrEP care, defined as having a minimum of 16 days with medication per month in 9 of 12 months per year, and reflects only the amount paid by the patient after insurance has been billed. Pharmacy type was defined as local specialty pharmacy (Y/N); local specialty pharmacies have specially trained staff that support patients with complex health conditions by assisting with medication access, coordinating financial assistance, guiding patients through their treatment, and supporting adherence. These pharmacies are located

on health system campuses, within medical office buildings, or are located in communities impacted by HIV. Non-specialty pharmacies are traditional retail pharmacies not typically affiliated with health systems.

A modified, annual PDC was calculated to determine an adherence threshold. Persons with at least 16 days of filled medication in each month were considered adherent for that month; if at least 9 of 12 months in the index year were classified as adherent (essentially, if annual PDC was >75%), then persons were considered adherent for the year. Persons who were adherent from initiation to 1 year of follow up and had at least 16 days of medication in each month after month 12 of follow up for at least 9 months in months 13-24 were considered adherent from 1 to 2 years of follow up; persons who were not considered adherent after the first 12 months were not included in this time period. Persons who were considered adherent from initiation to 1 year of follow up and from 1 to 2 years of follow up were considered adherent from initiation to 2 years of follow up. A PDC of 0.8 or greater is considered a general threshold for adherence, although for antiretrovirals used in the treatment of HIV the threshold is 0.9 (9, 24, 25). From these adherence thresholds, three outcomes were considered: adherent from initiation to 1 year of follow up, adherent from 1 to 2 years of follow up, and adherent from initiation to 2 years of follow up.

We used logistic regression to determine predictors of adherence in PrEP care for three models: one for each of the three periods of adherence. For multivariable model development, variables were included based on significance at the 0.1 level in bivariate analysis. Predictors were considered significant at the 0.05 level during multivariable analysis for inclusion in the final model. Collinearity was evaluated for each model, and model fit statistics were calculated using the Hosmer-Lemeshow test. All analyses were conducted using SAS Version 9.4 (SAS Institute). Data visualizations were conducted in Microsoft Excel 2016.

Results

Demographics

Among 7,148 persons who initiated PrEP in 2015 at a large national chain pharmacy, 97% were male and 3% were female (Table 1). The plurality (35%) were age 30-39, 22% were 25-29, 20% were 40-49, 12% were 50 or older, and 11% were 18-24. The mean monthly PrEP copay was $20 per person, with 77% paying a monthly PrEP copay of $20 or less. The majority had commercial insurance (80%), 15% had government insurance, and 5% had either cash, manufacturer's coupon, or 'other' denoted as their primary payer. Most did not attend a local specialty pharmacy (85%), with 15% that did.

Table 1. Demographic Characteristics of Patients Who Initiated HIV Pre-Exposure Prophylaxis in the United States, 2015 at Initiation

	n (%)
Total sample	7,148
Age	
18-24	784 (11%)
25-29	1552 (22%)
30-39	2521 (35%)
40-49	1432 (20%)
50+	855 (12%)
Gender	
Male	6900 (97%)
Female	244 (3%)
Monthly average copay	
$20 or less	5531 (77%)
More than $20	1614 (23%)
Mean (SD)	20 (78)
Payer (primary during entire period)	
Commercial	5699 (80%)
Government	1097 (15%)
Cash/Other	352 (5%)
Local specialty pharmacy	
Yes	1057 (15%)
No	6091 (85%)
Distance to pharmacy from home (miles)	
0 to <1 miles	5293 (74%)
1 to < 2 miles	1235 (17%)
2+ miles	620 (9%)
Mean (SD)	1 (3)
Urban/Rural Status	
Urban	3093 (43%)
Less dense urban	1458 (20%)
Suburban	2257 (32%)
Rural	340 (5%)

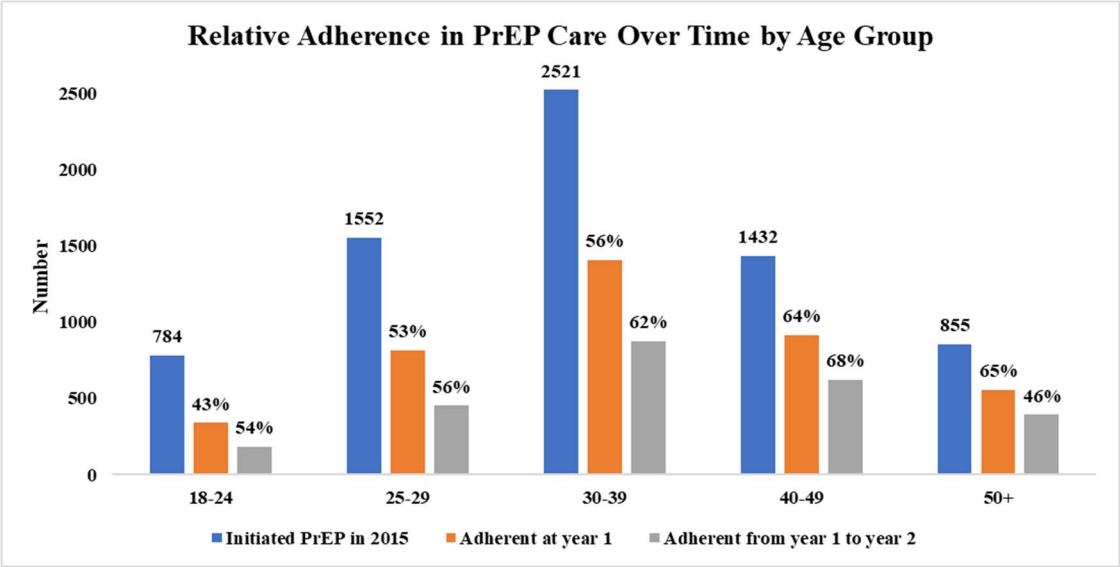
Adherence Characteristics

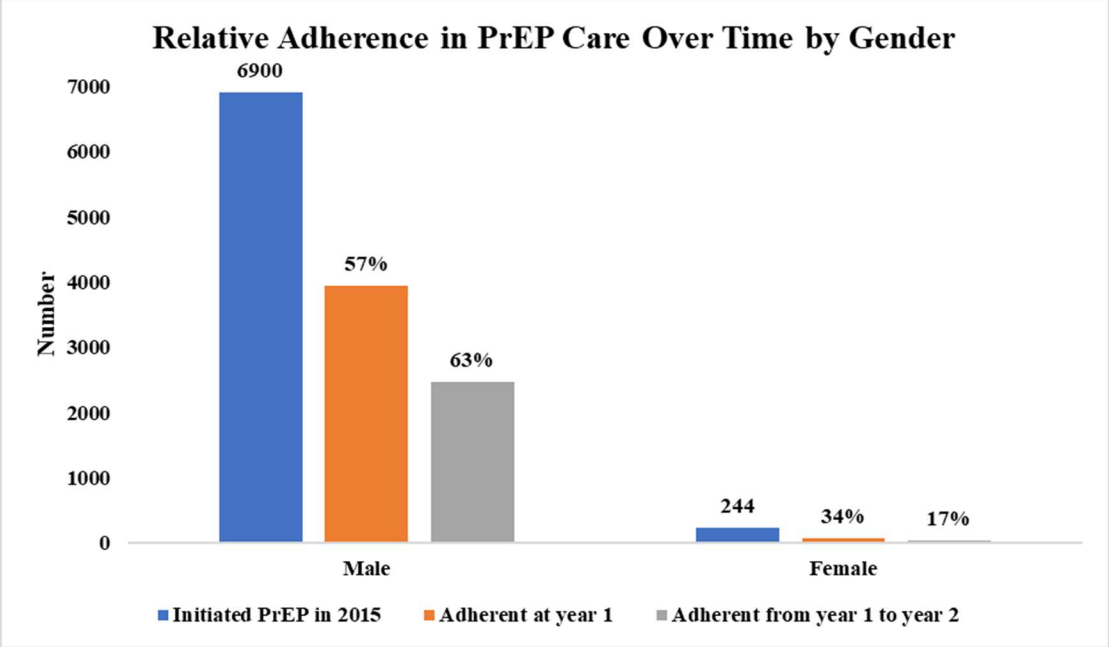
From initiation to 1 year of follow up 56% (4,030/7,148) were adherent in PrEP care, meeting the proportion of days covered threshold for at least 9 out of the 12 months in the period. From initiation to two years of follow up 35% (2,521/7,148) were adherent in PrEP care. The age category with the lowest adherence for both one-year follow-up periods was 18-24: 43% adherence from initiation to 1 year of follow up and 54% from 1 to 2 years of follow up (Table 2). Males had higher adherence than females for both one-year periods: 57% male versus 34% female adherence from initiation to 1 year of follow up and 63% male versus 49% female adherence from one to two years of follow up. Individuals with commercial insurance had higher adherence in both one-year periods than those with Medicare/Medicaid. See Figure 1.

Table 2. Adherence Characteristics of Patients Who Initiated HIV Pre-Exposure Prophylaxis in the United States, 2015

	PrEP Initiation	Adherent from Initiation to 1 Year of Follow Up		Adherent from 1 to 2 Years of Follow Up		Adherent from Initiation to 2 Years of Follow Up
	n = 7,144	n = 4,005 (56%)		n = 2,521 (63%)		n = 2,521 (35%)
	n	n	Adherence	n	Adherence	Adherence
Age						
18-24	784	339	43%	183	54%	23%
25-29	1552	815	53%	452	56%	29%
30-39	2521	1409	56%	872	62%	35%
40-49	1432	912	64%	621	68%	43%
50+	855	553	65%	392	71%	46%
Gender						
Male	6900	3944	57%	2479	63%	36%
Female	244	84	34%	41	49%	17%
Monthly average copay						
$20 or less	5531	3220	58%	2052	64%	37%
More than $20	1614	808	50%	468	58%	29%
Payer (primary during entire period)						
Commercial	5699	3366	59%	2165	64%	38%
Government	1097	506	46%	267	53%	24%
Cash/Other	352	158	45%	89	56%	25%
Local specialty pharmacy						
Yes	1057	673	64%	442	66%	42%
No	6091	3357	55%	2079	62%	34%

Figure 1: Adherence in PrEP care over time by age group (top) and gender (bottom)





Overall, adherence rates were slightly higher (63% versus 56%) from 1 to 2 years of follow up than from initiation to 1 year of follow up. See Table 2. Those who were not adherent from initiation to one year of follow up were excluded from one year to two years of follow up for the analysis; however, there were 5% (n=369) who initiated PrEP in 2015 and were not adherent in the first year of follow up but would have been considered adherent in the second year. This indicates a low rate of returning to PrEP care after becoming nonadherent.

Predictors of Refill Adherence

Table 3 shows bivariate and multivariable logistic regressions of adherence from initiation to 1 year of follow up, 1 to two years of follow up, and from initiation to 2 years of follow up on independent variables. Significant bivariate associations were the same for each of the three outcomes, and included age, gender, average monthly copay, primary payer, and pharmacy type. Urban/rural status and distance in miles from the patient's address to the closest pharmacy were not included in the multivariable models.

In multivariable analysis, Table 3, being older than 18-24 years (25-29 aOR 1.43, 95% CI: 1.20-1.71; 30-39 aOR 1.66, 95% CI: 1.41-1.96; 40-49 aOR 2.37, 95% CI: 1.98-2.84; 50+ aOR 2.57, 95% CI: 2.10-3.15), being male (aOR 2.25, 95% CI: 1.70-2.97), having a copay of $20 or less (aOR 0.63, 95% CI: 0.56-0.71), having commercial insurance (government aOR 0.58, 95% CI: 0.50-0.67; cash/other aOR 0.54, 95% CI 0.44-0.68), and attending a local specialty pharmacy (aOR 1.42, 95% CI: 1.24-1.64) were statistically significantly associated with adherence from initiation to 1 year of follow up. The same predictors were statistically significantly associated with adherence from 1 to 2 years of follow up: being older than 18-24 years (25-29 aOR 1.14, 95% CI: 0.89-1.47; 30-39 aOR 1.57, 95% CI: 1.24-1.99; 40-49 aOR 2.53, 95% CI: 1.95-3.27; 50+ aOR 2.68, 95% CI: 2.02-3.55), being male (aOR 1.93, 95% CI: 1.25-2.98), having a copay of $20 or less (aOR 0.71, 95% CI: 0.60- 0.84), having commercial insurance (government aOR 0.59, 95% CI: 0.48-0.72; cash/other aOR 0.64, 95% CI 0.46-0.88),

and attending a local specialty pharmacy (aOR 1.31, 95% CI: 1.09-1.57). Similarly, being older than 18-24 years (25-29 aOR 1.32, 95% CI: 1.08-1.61; 30-39 aOR 1.72, 95% CI: 1.43-2.08; 40-49 aOR 2.57, 95% CI: 2.11-3.14; 50+ aOR 2.97, 95% CI: 2.40-3.71), being male (aOR 2.36, 95% CI: 1.67- 3.35), having a copay of $20 or less (aOR 0.60, 95% CI: 0.53- 0.68), having commercial insurance (government aOR 0.50, 95% CI: 0.43-0.59; cash/other aOR 0.53, 95% CI 0.41-0.68), and attending a local specialty pharmacy (aOR 1.38, 95% CI: 1.20-1.58) were statistically significantly associated with adherence from initiation to 2 years of follow up.

Table 3. Factors Associated with Adherence in PrEP Care from Initiation to 1 Year of Follow Up, 1 to 2 Years of Follow Up, and Initiation to 2 Years of Follow Up Among Patients Who Initiated PrEP in the United States, 2015

	Adherent from Initiation to 1 Year of Follow Up n = 7,144		**Adherent from 1 to 2 Years of Follow Up n = 4,005**		**Adherent from Initiation to 2 Years of Follow Up n = 7,144**	
	Bivariate OR (95% CI)	Multivariable aOR (95% CI)	Bivariate OR (95% CI)	Multivariable aOR (95% CI)	Bivariate OR (95% CI)	Multivariable aOR (95% CI)
Age						
18-24	Ref	Ref	Ref	Ref	Ref	Ref
25-29	1.45 (1.22, 1.73)	1.43 (1.20, 1.71)	1.16 (0.90, 1.48)	1.14 (0.89, 1.47)	1.35 (1.11, 1.65)	1.32 (1.08, 1.61)
30-39	1.66 (1.42, 1.96)	1.66 (1.41, 1.96)	1.58 (1.25, 1.99)	1.57 (1.24, 1.99)	1.74 (1.44, 2.09)	1.72 (1.43, 2.08)
40-49	2.30 (1.93, 2.75)	2.37 (1.98, 2.84)	2.48 (1.92, 3.20)	2.53 (1.95, 3.27)	2.52 (2.07, 3.06)	2.57 (2.11, 3.14)
50+	2.40 (1.97, 2.93)	2.57 (2.10, 3.15)	2.48 (1.88, 3.27)	2.68 (2.02, 3.55)	2.78 (2.25, 3.44)	2.98 (2.40, 3.71)
Gender						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	2.54 (1.94, 3.32)	2.25 (1.70, 2.97)	2.11 (1.39, 3.20)	1.93 (1.25, 2.98)	2.78 (1.98, 3.90)	2.36 (1.67, 3.35)
Monthly average copay						
$20 or less	Ref	Ref	Ref	Ref	Ref	Ref
More than $20	0.72 (0.64, 0.80)	0.63 (0.56, 0.71)	0.79 (0.68, 0.93)	0.71 (0.60, 0.84)	0.69 (0.61, 0.78)	0.60 (0.53, 0.68)
Payer (primary during entire period)						
Commercial	Ref	Ref	Ref	Ref	Ref	Ref
Government	0.59 (0.52, 0.68)	0.58 (0.50, 0.67)	0.60 (0.50, 0.72)	0.59 (0.48, 0.72)	0.53 (0.45, 0.61)	0.50 (0.43, 0.59)
Cash/Other	0.56 (0.46, 0.70)	0.54 (0.44, 0.68)	0.64 (0.47, 0.88)	0.64 (0.46, 0.88)	0.55 (0.43, 0.71)	0.53 (0.41, 0.68)
Local specialty pharmacy						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.43 (1.25, 1.63)	1.42 (1.24, 1.64)	1.29 (1.08, 1.54)	1.31 (1.09, 1.57)	1.39 (1.21, 1.59)	1.38 (1.20, 1.58)
Distance to pharmacy from home (miles)	NS		NS		NS	
Urban/Rural Status	NS		NS		NS	

NS=not significant at the $p < 0.05$ level

Discussion

In the largest study to date of PrEP retention over a two-year time period, we observed 56% adherence from initiation to 1 year of follow up and 63% adherence from 1 to 2 years of follow up, with 35% adherent from initiation to 2 years of follow up. There are substantial rates of drop off from care both from initiation to the first year of follow up as well as in the second year of follow up of adherence to PrEP. Increased odds of adherence to PrEP care were observed across the 2-year period with increasing age, male gender, having a copay of $20 or less, having commercial insurance, and attending a local specialty pharmacy. Low adherence at 2-years of follow up suggests that many individuals have problems in maintaining long term PrEP adherence. To improve adherence over time, programs and providers offering PrEP services should address known barriers to care such as motivation and environmental access barriers (26). Improved HIV risk reduction counseling has been suggested to improve adherence and retention in care of people who would otherwise drop out (27, 28).

The age group that has the lowest odds of retention is the age group that is most indicated for PrEP: 18- to 24-year-olds (29, 30). This group may be less likely to request PrEP than older adults, experience more challenges with benefit and cost navigation, fear unwarranted disclosure through the utilization of parental insurance, have limited knowledge of and experience with the healthcare system, and face significant financial barriers (30, 31). The long-term success of PrEP adherence depends on young people, particularly young MSM, having access to comprehensive HIV primary prevention services (such as counselling, free condoms, STI treatment, and HIV testing) being available at low or no cost to this age group (32). Many of these services are available from community organizations or non-profits in certain areas, but do not cover all individuals facing access barriers.

Consistent with previous PrEP studies that included both men and women, we found that men had higher odds of being adherent in PrEP care over time (17, 33, 34). Multiple PrEP studies

have found that women consistently underestimate their risk for acquiring HIV, a likely factor in PrEP non-adherence and discontinuation; they suggest that risk-focused HIV counseling could help bridge that gap and support adherence and retention in PrEP care (35, 36). Programs and providers offering PrEP services should be aware of disparities between men and women in both adherence and retention and seek to address concerns that may be specific to women to enhance female retention in PrEP care.

Lower copays have been associated with improved patient outcomes, including adherence and retention in care, in numerous studies (37). We found that patients with a copay of $20 or less had higher odds of retention at one and two years of follow up than patients with higher copays. To be included in this analysis, however, individuals needed to be able to make their first copayment and complete their first fill. Persons who could not afford a high first copayment therefore never entered the dataset. This means that our findings do not address individuals who were unable to initiate PrEP due to financial barriers. People who are uninsured or underinsured are more likely to have a copay that they could not make, while people with better coverage are more likely to have a usual source of care and be able to afford needed care (38), so the impact of primary payer on adherence over time is likely underestimated. Based on our data, programs that expand financial assistance to decrease patient cost should be investigated as mechanisms to improve adherence over time.

We found that primary payer was a significant predictor of retention, with commercial patients making up the largest proportion of the patient population and having the highest odds of retention. There is a mixed consensus in the literature on the role of insurer on medication adherence and persistence, with some studies identifying lack of insurance as a barrier (4) and others not finding a significant difference between government insurance and commercial insurance in terms of patient outcomes (38). Other PrEP studies have been of people in a commercially insured database and have not been able to make this comparison (39, 40). With

copay assistance and lowered financial burden on the patient, the impact of insurance type may be partially mitigated, with increased retention of un- and underinsured patients.

Limitations

There are several limitations to this study. The biggest limitation is the inability to identify individuals who are no longer filling prescriptions at Walgreens, which may make adherence rates appear lower than they are. Secondly, the study population is from a single large national chain pharmacy, and individuals from this group are unlikely to be representative of all PrEP users in the United States. There may be selection bias introduced by the observational nature of this dataset and known inconsistencies in the US healthcare system. Persons who use TDF-FTC for chronic Hepatitis B management may be included in the present sample. In order to have been included in this analysis, a patient must have filled at least 60 days of TDF-FTC, so patients unable to make their first or second copay are not included. Medicaid and Medicare are both included in the government insurance category; because Medicaid has low copays by design, this category may need to be separated in the future to get a better measure of the impact of insurance type on retention in care. Additionally, our findings may be impacted by the calculation of our copay variable; if a patient were to experience an increase in copay after several months of care, then the calculated average monthly copay would not be reflective of this change. Manufacturer's coupons, HSA savings dollars, or copay assistance may offset higher copays, introducing information bias. Additionally, some patients could have used a manufacturer's coupon until the funds were depleted, and then they may have dropped out of care; although only 1% of the sample (n=77) used a manufacturer's card as their primary method of payment, the proportion of those using a manufacturer's card as a secondary or supplemental method of payment was not calculated. Some of the individual payer codes in the cash/other category are unknown.

Urban/rural status and distance to nearest pharmacy in this chain from patient's address were not significant predictors of retention in PrEP care. In light of urban/rural health disparities and cultural differences in HIV care, we expected to see an impact on retention in care from this predictor (41). The distance to nearest pharmacy variable was calculated using the pharmacy nearest to the patient's home of record, not the pharmacy at which they fill most often, potentially introducing bias in this measure.

Because these data are from a pharmacy claims database, some variables, including race/ethnicity, income, sexual orientation, and gender identity, were not available. This is a significant limitation for a population-based study.

Conclusions

Using pharmacy refill data to measure adherence to PrEP care over 2 years of follow up, we found suboptimal adherence from initiation to 1 year of follow up, from 1 to 2 years of follow up, and from initiation to 2 years of follow up due to a combination of demographic, financial, and pharmacy factors. PrEP interventions targeted at women and young adults, improved HIV risk reduction counseling and reduced patient cost sharing are likely needed to reach patients and improve long-term adherence, thus decreasing risks for HIV. Further research is needed to explore how social, structural, or individual factors may undermine or enhance adherence to PrEP and retention in PrEP care.

References

1. Baeten J, Celum C. Oral antiretroviral chemoprophylaxis: current status. *Curr Opin HIV AIDS* 2012;7(6):514-9.
2. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363(27):2587-99.
3. Donnell D, Baeten JM, Bumpus NN, et al. HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention. *J Acquir Immune Defic Syndr* 2014;66(3):340-8.
4. Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. *JAMA Intern Med* 2016;176(1):75-84.
5. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012;367(5):399-410.
6. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012;367(5):423-34.
7. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016;387(10013):53-60.
8. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med* 2015;373(23):2237-46.
9. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;119(23):3028-35.
10. Baeten JM, Haberer JE, Liu AY, et al. Preexposure prophylaxis for HIV prevention: where have we been and where are we going? *J Acquir Immune Defic Syndr* 2013;63 Suppl 2:S122-9.

11. Blashill AJ, Ehlinger PP, Mayer KH, et al. Optimizing adherence to preexposure and postexposure prophylaxis: the need for an integrated biobehavioral approach. *Clin Infect Dis* 2015;60 Suppl 3:S187-90.

12. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015;372(6):509-18.

13. Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection among African Women. *N Engl J Med* 2012;367(5):411-22.

14. Liu AY, Hessol NA, Vittinghoff E, et al. Medication adherence among men who have sex with men at risk for HIV infection in the United States: implications for pre-exposure prophylaxis implementation. *AIDS Patient Care STDS* 2014;28(12):622-7.

15. Chan PA, Mena L, Patel R, et al. Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among men who have sex with men in three US cities. *J Int AIDS Soc* 2016;19(1):20903.

16. Doblecki-Lewis S, Liu A, Feaster D, et al. Healthcare Access and PrEP Continuation in San Francisco and Miami After the US PrEP Demo Project. *J Acquir Immune Defic Syndr* 2017;74(5):531-8.

17. Marcus JL, Hurley LB, Hare CB, et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. *J Acquir Immune Defic Syndr* 2016;73(5):540-6.

18. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. *J Clin Epidemiol* 2004;57(10):1107-10.

19. Amico KR, Marcus JL, McMahan V, et al. Study product adherence measurement in the iPrEx placebo-controlled trial: concordance with drug detection. *J Acquir Immune Defic Syndr* 2014;66(5):530-7.

20. Bezabhe WM, Peterson GM, Bereznicki L, et al. Adherence to antiretroviral drug therapy in adult patients who are HIV-positive in Northwest Ethiopia: a study protocol. *BMJ Open* 2013;3(10):e003559.

21. Salinas JL, Alave JL, Westfall AO, et al. Medication possession ratio predicts antiretroviral regimens persistence in Peru. *PLoS One* 2013;8(10):e76323.

22. Holtzman CW, Brady KA, Yehia BR. Retention in care and medication adherence: current challenges to antiretroviral therapy success. *Drugs* 2015;75(5):445-54.

23. Williams AB, Amico KR, Bova C, et al. A proposal for quality standards for measuring medication adherence in research. *AIDS Behav* 2013;17(1):284-97.

24. Nau DP. Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence. *Pharmacy Quality Alliance* 2012.

25. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J* 2008;155(4):772-9.

26. Taylor SW, Mayer KH, Elsesser SM, et al. Optimizing Content for Pre-exposure Prophylaxis (PrEP) Counseling for Men Who Have Sex with Men: Perspectives of PrEP Users and High-Risk PrEP Naive Men. *AIDS Behav* 2014;18:871-79.

27. Underhill K, Guthrie KM, Colleran C, et al. Temporal Fluctuations in Behavior, Perceived HIV Risk, and Willingness to Use Pre-Exposure Prophylaxis (PrEP). *Arch Sex Behav* 2018.

28. Namey E, Agot K, Ahmed K, et al. When and why women might suspend PrEP use according to perceived seasons of risk: implications for PrEP-specific risk-reduction counselling. *Cult Health Sex* 2016;18(9):1081-91.

29. Paltiel AD, Freedberg KA, Scott CA, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. *Clin Infect Dis* 2009;48(6):806-15.

30. Hosek S, Celum C, Wilson CM, et al. Preventing HIV among adolescents with oral PrEP: observations and challenges in the United States and South Africa. *J Int AIDS Soc* 2016;19(7(Suppl 6)):21107.

31. Hosek SG, Siberry G, Bell M, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. *J Acquir Immune Defic Syndr* 2013;62(4):447-56.

32. Bauermeister JA, Meanley S, Pingel E, et al. PrEP awareness and perceived barriers among single young men who have sex with men. *Curr HIV Res* 2013;11(7):520-7.

33. Haberer JE, Baeten JM, Campbell J, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. *PLoS Med* 2013;10(9):e1001511.

34. Blackstock OJ, Patel VV, Felsen U, et al. Pre-exposure prophylaxis prescribing and retention in care among heterosexual women at a community-based comprehensive sexual health clinic. *AIDS Care* 2017;29(7):866-9.

35. Koenig LJ, Lyles C, Smith DK. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis: lessons learned from trials and treatment studies. *Am J Prev Med* 2013;44(1 Suppl 2):S91-8.

36. Garfinkel DB, Alexander KA, McDonald-Mosley R, et al. Predictors of HIV-related risk perception and PrEP acceptability among young adult female family planning patients. *AIDS Care* 2017;29(6):751-8.

37. Eaddy MT, Cook CL, O'Day K, et al. How patient cost-sharing trends affect adherence and outcomes: a literature review. *P T* 2012;37(1):45-55.

38. Sommers BD, Gawande AA, Baicker K. Health Insurance Coverage and Health. *N Engl J Med* 2017;377(20):2000-1.

39. Wu H, Mendoza MC, Huang YA, et al. Uptake of HIV Preexposure Prophylaxis Among Commercially Insured Persons-United States, 2010-2014. *Clin Infect Dis* 2017;64(2):144-9.

40. Briesacher BA, Andrade SE, Fouayzi H, et al. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy* 2008;28(4):437-43.

41. Bowen AM, Horvath K, Williams ML. A randomized control trial of Internet-delivered HIV prevention targeting rural MSM. *Health Educ Res* 2007;22(1):120-7.