

Persistence With Human Immunodeficiency Virus Pre-exposure Prophylaxis in the United States, 2012–2017

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(See the Editorial Commentary by Siegler on pages 386–7.)

Background. Daily oral pre-exposure prophylaxis (PrEP) is highly effective in preventing human immunodeficiency virus (HIV) infection if used adherently throughout periods of HIV risk. We estimated PrEP persistence among cohorts of persons with commercial or Medicaid insurance.

Methods. We analyzed data from the IBM MarketScan Research Database to identify persons aged 18–64 years who initiated PrEP between 2012 and 2017. We assessed PrEP persistence by calculating the time period that each person continued filling PrEP prescriptions until there was a gap in prescription fills > 30 days. We used Kaplan-Meier time-to-event methods to estimate the proportion of PrEP users who persisted with PrEP at 3, 6, and 12 months after initiation, and constructed Cox proportional hazards models to determine patient characteristics associated with nonpersistence.

Results. We studied 11 807 commercially insured and 647 Medicaid insured persons with PrEP prescriptions. Commercially insured patients persisted for a median time of 13.7 months (95% confidence interval [CI], 13.3–14.1), compared to 6.8 months (95% CI, 6.1–7.6) among Medicaid patients. Additionally, female sex, younger age, residence in rural location, and black race were associated with shorter persistence. After adjusting for covariates, we found that female sex (hazard ratio [HR], 1.81 [95% CI, 1.56–2.11]) and younger age (18–24 years: HR, 2.38 [95% CI, 2.11–2.69]) predicted nonpersistence.

Conclusions. More than half of commercially insured persons who initiated PrEP persisted with it for 12 months, compared to a third of those with Medicaid. A better understanding of reasons for nonpersistence is important to support persistent PrEP use and to develop interventions designed for the diverse needs of at-risk populations.

Keywords. PrEP; pre-exposure prophylaxis; persistence; medication use; prescription fill.

Human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) with a daily dose of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) is an effective biomedical intervention to prevent acquisition of HIV infection. One of the key strategies in the federal Ending the HIV Epidemic initiative is to expand PrEP use among at-risk persons to prevent them from acquiring HIV infection [1]. The Centers for Disease Control and Prevention (CDC) recommends PrEP for adolescent and adults who report sexual or injection behaviors that increase risk of HIV exposure, including men who have sex with men (MSM); heterosexual men and women who are in networks and communities with a high prevalence of HIV; and persons who inject drugs [2, 3]. The United States (US) Preventive Services Task Force also recommends clinicians offer PrEP to persons at high risk of acquiring HIV [4]. It is estimated that approximately 1.1 million persons in the United States are at risk of

HIV acquisition and could benefit from taking PrEP [5], yet only 7% received a PrEP prescription in 2016 [6].

High adherence to daily PrEP is associated with high prevention effectiveness, with at least 4 doses per week providing > 90% efficacy for MSM [7]. In clinical trials, poor adherence was associated with markedly reduced efficacy of PrEP [8, 9]. Poor adherence to TDF/FTC also can lead to HIV drug resistance if the person becomes infected while using PrEP [10]. It is important that persons persist with PrEP during periods of time when they might be at increased risk of acquiring HIV. If PrEP is not used consistently during these periods, exposure to HIV can result in an infection.

Medication adherence and medication persistence both serve to measure a patient's deviation from the recommended use of prescribed medications but are 2 different constructs [11]. Medication adherence refers to how closely a patient follows the dosing regimen recommended by their healthcare providers [12]. Medication persistence refers to the length of time with consistent refills. A patient needs to first refill their prescriptions to be adherent, and nonpersistence will result in extended periods of nonadherence [13]. Persistent PrEP use during periods of HIV risk is also important for HIV prevention because the protective effect of PrEP wanes over 7–10 days after

Received 2 October 2019; editorial decision 27 November 2019; accepted 13 January 2020; published online January 14, 2020.

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Clinical Infectious Diseases® 2021;72(3):379–85

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DOI: 10.1093/cid/ciaa037

discontinuation [14, 15] and persons can acquire HIV infection soon after PrEP is discontinued [16].

Previous studies that assessed PrEP persistence have been demonstration projects or studies in closed healthcare systems, limiting the generalization of the study findings [17–21]. The objective of this study was to estimate PrEP persistence among cohorts of PrEP users with commercial or Medicaid health insurance constructed using large health services databases, and associations between PrEP persistence and characteristics of PrEP users.

METHODS

Data Source

We analyzed data from 2 separate databases, the IBM MarketScan Commercial Claims and Encounter (hereafter referred to as commercial) database and the IBM MarketScan Multi-State Medicaid (hereafter referred to as Medicaid) database. The commercial database was a nationwide convenience sample overrepresenting households with higher income in the United States. It included approximately 30 million annual enrollees from 350 employer-sponsored commercial health plans, and represented about 20% of the US commercially insured population. The Medicaid database included approximately 8–13 million Medicaid annual enrollees from 8–10 unidentified states, accounting for nearly one-fifth of Medicaid enrollees in the United States. Both databases allowed longitudinal tracking at the person level, and included information for patient age, sex, and health plan enrollment history, as well as paid and adjudicated health services claims for diagnoses, procedures, and prescriptions dispensed. Geographic information such as region or Metropolitan Statistical Area was included in the commercial database but not in the Medicaid database. An urban location was defined as a Metropolitan Statistical Area that consisted of 1 or more counties with a city of $\geq 50\,000$ inhabitants. Race/ethnicity data were included in only the Medicaid database.

Study Sample

We identified PrEP users who filled their first PrEP prescription between 2012 and 2017 using an algorithm we previously developed and validated [22, 23]. Among persons aged 18–64 years, we selected those with at least 1 TDF/FTC prescription during our study period of 1 January 2012 and 31 December 2017, and excluded persons with prior HIV or hepatitis B (HBV) infection identified by diagnostic and prescription codes that indicated HIV or HBV infection. The remaining persons who were prescribed TDF/FTC continuously for > 30 days were categorized as PrEP users, and we assumed the date of the first TDF/FTC prescription was their PrEP initiation date.

We created 2 cohorts of PrEP users from the databases—a cohort of commercially insured users and a cohort of Medicaid-insured users. We restricted the sample of PrEP users to those continuously enrolled in their health plans for at least 6 months

before and 6 months after the first prescription date to ensure no lapse in insurance coverage and healthcare services data. In addition, a minimum of a 6-month observation period after PrEP initiation allowed sufficient time to assess PrEP persistence. We assessed the demographic characteristics of persons in each cohort.

Measuring Persistence

We defined persistence as the length of time that a person continued to refill PrEP prescriptions without an interruption of > 30 days. We monitored PrEP prescription refills from a person's first PrEP prescription date until there was a gap > 30 days between refills, or a complete discontinuation of PrEP. We calculated the end date in PrEP persistence as the date the prescribed supply of pills would be depleted if taken daily. If the person did not refill a TDF/FTC prescription within 30 days of the end date, we considered the person nonpersistent on the 31st day. We used a 30-day gap to define nonpersistence because a longer gap might result in drug levels too low to confer protection. In a sensitivity analysis, we used a gap of > 90 days to assess the robustness of our study results. Although persons might have reinitiated PrEP after nonpersistence, we only included their first episode of PrEP use in our study.

Statistical Analysis

We performed separate analyses for the commercial cohort and the Medicaid cohort using SAS version 9.4 software (SAS Institute, Cary, North Carolina). We used the Kaplan-Meier time-to-event method to estimate the median duration of persistence in months, and determined the percentage of PrEP users who were persistent at 3, 6, and 12 months since PrEP initiation. We censored observations from users if one of the following events occurred prior to the date they were considered nonpersistent: disenrollment from the health plan, an HIV diagnosis, an antiretroviral prescription other than TDF/FTC, or the end of study period. We generated Kaplan-Meier survival curves of PrEP persistence for each subgroup of sex, age group, urban vs rural location, and region for commercially insured users; and sex, age group, and race/ethnicity for Medicaid-insured users. We tested for homogeneity using the log-rank test. We also compared the Kaplan-Meier curves of both cohorts and tested the homogeneity between commercial and Medicaid cohorts. Additionally, we used Cox proportional hazard regression models to estimate the associations between PrEP users' characteristics and nonpersistence after adjusting for covariates. We included age, sex, urban vs rural location, and region in the commercial model; and age, sex, and race/ethnicity in the Medicaid model.

RESULTS

During 2012–2017, we identified 11 807 commercially insured PrEP users and 647 Medicaid-insured PrEP users who met inclusion criteria for the analysis (Supplementary Appendix Table 1).

In the commercial cohort, most were male (97.7%), aged 25–44 years (60.8%), and resided in urban areas (95.2%). In the Medicaid cohort, 77.6% were male, and 63.2% were aged between 25 and 44 years. Among Medicaid-insured PrEP users, 282 were white (43.6%), 167 were black (25.8%), and 162 were categorized as other race/ethnicity (25.0%) including 8 Hispanic persons (Supplementary Appendix Table 2).

Overall, the median persistence of commercially insured PrEP users was 13.7 months (95% confidence interval [CI], 13.3–14.1), 2 times as high as the median persistence among Medicaid-insured PrEP users of 6.8 months (95% CI, 6.1–7.6) ($P < .0001$). After starting PrEP, 54.0% of commercially insured users and 29.9% of Medicaid users persisted with PrEP for 12 months (Table 1 and Figure 1).

Male users persisted longer than female users. The median persistence among commercially insured women was 6.8 months (95% CI, 5.6–8.7), compared to 13.9 months (95% CI, 13.4–14.3) among commercially insured men. At 12 months

after PrEP initiation, 36.7% of the commercially insured women persisted with PrEP medications, compared to 54.4% of the commercially insured men. Women aged 18–44 years persisted for a median of 5.6 months (95% CI, 4.5–6.9) compared to women aged 45–64 years who persisted for 12.2 months (95% CI, 10.2–16.1) (data not shown). For Medicaid PrEP users, the median persistence was 5.8 months (95% CI, 4.1–7.1) for women and 7.1 months (95% CI, 6.2–8.1) for men. At 12 months after PrEP initiation, 20.8% of the Medicaid-insured women persisted with PrEP, compared to 32.4% of the Medicaid-insured men (Table 1).

Among commercially insured PrEP users, the age-stratified Kaplan-Meier curves indicated that PrEP persistence increased with age ($P < .0001$), and the youngest group persisted for the least time (Figure 2). The median persistence was 18.9 months (95% CI, 17.6–20.6) for users aged 45–54 years, and 7.4 months (95% CI, 6.9–8.2) for users aged 18–24 years. At 12 months, 62.9% of users in the age group of 45–54 years vs 35.0% of users

Table 1. Percentage of Patients Aged 18–64 Years Using Human Immunodeficiency Virus Pre-exposure Prophylaxis (PrEP) Who Were Persistent With PrEP for 3, 6, or 12 Months and Their Median Persistence by Insurance Type and Demographic Characteristics, 2012–2017

Characteristic	No.	PrEP Persistence (%)			Median Persistence, mo	(95% CI)	P Value ^a
		3 mo	6 mo	12 mo			
Commercially insured PrEP patients							
Overall	11 807	87.1	73.3	54.0	13.7	(13.3–14.1)	
Sex							<.0001
Male	11 541	87.4	73.7	54.4	13.9	(13.4–14.3)	
Female	266	74.1	54.6	36.7	6.8	(5.6–8.7)	
Age group, y							<.0001
18–24	1463	78.0	58.7	35.0	7.4	(6.9–8.2)	
25–34	4145	86.9	71.3	50.6	12.2	(11.7–12.7)	
35–44	3037	88.7	76.7	57.9	15.4	(14.6–16.4)	
45–54	2366	90.2	78.9	62.9	18.9	(17.6–20.6)	
55–64	796	89.7	80.9	64.3	18.4	(16.8–21.6)	
Urban or rural location							.0163
Urban	11 235	87.3	73.6	54.3	13.9	(13.4–14.3)	
Rural	287	83.2	66.3	48.7	11.3	(9.8–14.3)	
Medicaid-insured PrEP patients							
Overall	647	79.1	54.2	29.9	6.8	(6.1–7.6)	
Sex							.0011
Male	502	81.6	55.8	32.4	7.1	(6.2–8.1)	
Female	145	70.2	49.0	20.8	5.8	(4.1–7.1)	
Age, y							.0109
18–24	117	74.2	45.2	16.8	5.1	(4.0–6.7)	
25–34	259	76.9	51.9	30.3	6.3	(5.5–8.0)	
35–44	150	83.6	59.1	31.8	7.1	(6.1–8.5)	
45–54	91	81.8	64.0	34.1	8.9	(7.3–10.6)	
55–64	30	86.2	58.2	45.7	9.7	(4.3–13.5)	
Race/ethnicity							.0028
White	282	82.0	57.5	33.0	7.3	(6.3–8.5)	
Black	167	69.7	44.1	21.6	4.7	(4.0–6.2)	
Other ^b	162	83.7	61.1	35.2	8.0	(6.3–9.6)	

Abbreviations: CI, confidence interval; NA, not applicable; PrEP, pre-exposure prophylaxis.

^aLog-rank tests were used to compare survival distributions within groups.

^bOther includes 8 Hispanic persons.

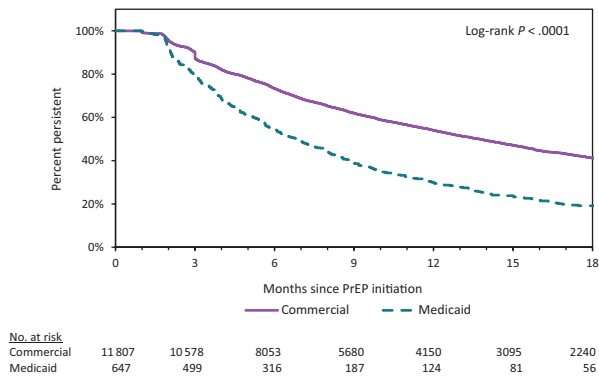


Figure 1. Kaplan-Meier curves of percentage of patients aged 18–64 years using human immunodeficiency virus pre-exposure prophylaxis (PrEP) who persisted with PrEP, by insurance type, 2012–2017.

in the youngest age group were persistent. We observed the similar trend among Medicaid-insured users that younger users persisted for less time than older users. The median persistence was 8.9 months (95% CI, 7.3–10.6) for users aged 45–54 years, and 5.1 months (95% CI, 4.0–6.7) for users aged 18–24 years (Table 1).

Among Medicaid-insured PrEP users, the median persistence of black users was 4.7 months (95% CI, 4.0–6.2), which was significantly shorter than the median persistence of white users (7.3 months) and users of other race/ethnicity (8.0 months) ($P = .0028$; Figure 3).

Among commercially insured PrEP users, we found in our multivariable model of nonpersistence that compared to male users and users in the oldest age group, female users (hazard ratio [HR], 1.81; $P < .0001$) and younger users were less likely

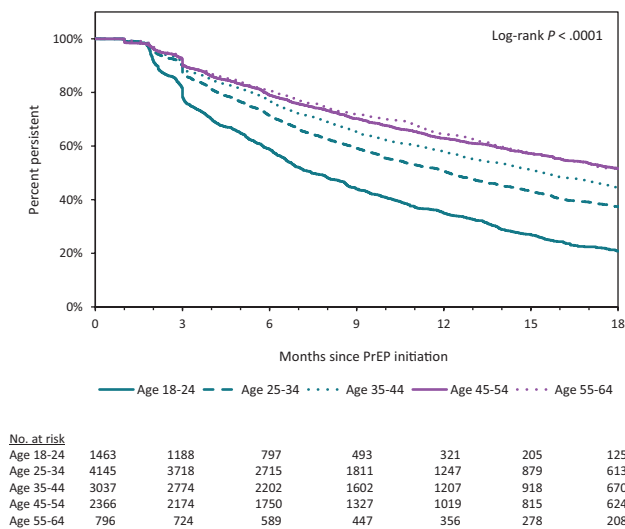


Figure 2. Kaplan-Meier curves of percentage of commercially insured patients aged 18–64 years using human immunodeficiency virus pre-exposure prophylaxis (PrEP) who persisted with PrEP, by age group, 2012–2017.

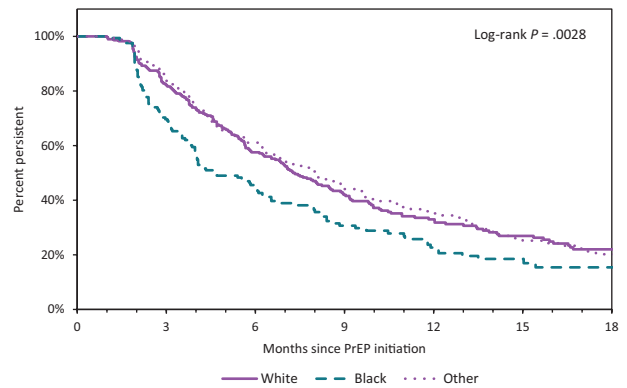


Figure 3. Kaplan-Meier curves of percentage of Medicaid patients aged 18–64 years using human immunodeficiency virus pre-exposure prophylaxis (PrEP) who persisted with PrEP, by race, 2012–2017.

to persist with PrEP. Persons aged 18–24 years were 2.4 times as likely to not persist compared to persons aged 55–64 years (HR, 2.38; $P < .0001$). Among Medicaid PrEP users, we found in our multivariable model that female sex (HR, 1.47; $P = .0011$) and the youngest age group (HR, 1.70; $P = .0331$) were associated with nonpersistence. Although black users had a higher hazard ratio (HR, 1.22) than white or other users, the difference was not statistically significant ($P = .0861$) in the multivariable model (Table 2).

In our sensitivity analysis, defining nonpersistence using a gap > 90 days resulted in a longer median persistence because some users who stopped PrEP restarted it within 90 days and were recategorized with longer persistence (Supplementary Appendix Table 3). Nevertheless, we observed similar trends in persistence among the subgroups, with women and younger persons persisting for less time compared to men and older persons. (Supplementary Appendix Tables 4 and 5).

DISCUSSION

We found that PrEP users with Medicaid insurance persisted with PrEP for a median of 7 months, half of the time of 14 months among users with commercial insurance. We also observed that more than half of commercially insured persons who started PrEP persisted for at least 12 months, compared to only a third of Medicaid-insured persons. In our study, female sex, younger age, rural residence, and black race/ethnicity were independently associated with shorter periods of PrEP use; and female sex and younger age predicted nonpersistence after adjusting other factors. Previous studies have identified similar patient factors associated with PrEP discontinuation, including female sex, younger age, black race/ethnicity, and uninsured status [17–20, 24]. A recent study of PrEP prescriptions dispensed by a national pharmacy chain also found that more

Table 2. Cox Proportional Hazard Models of Nonpersistence With Human Immunodeficiency Virus Pre-exposure Prophylaxis Since Initiation Among Patients Aged 18–64 Years by Insurance Type and Demographic Characteristics, 2012–2017

Characteristic	Commercial PrEP Patients			Medicaid PrEP Patients		
	HR ^a	(95% CI)	P Value	HR ^a	(95% CI)	P Value
Sex						
Male	Ref	...		Ref	...	
Female	1.81	(1.56–2.11)	<.0001	1.47	(1.17–1.85)	.0011
Age group, y						
18–24	2.38	(2.11–2.69)	<.0001	1.70	(1.04–2.78)	.0331
25–34	1.50	(1.34–1.68)	<.0001	1.28	(.81–2.03)	.2941
35–44	1.23	(1.10–1.38)	<.0004	1.21	(.75–1.94)	.4420
45–54	1.01	(.90–1.14)	.8613	0.89	(.53–1.48)	.6439
55–64	Ref	...		Ref	...	
Race/ethnicity						
White	NA	...		Ref	...	
Black	NA	...		1.22	(.97–1.54)	.0861
Other ^b	NA	...		0.97	(.78–1.22)	.8022
Urban or rural location						
Urban	Ref	...		NA	...	
Rural	1.14	(.98–1.34)	.0912	NA	...	
Region						
Northeast	Ref	...		NA	...	
Midwest	0.95	(.88–1.03)	.2354	NA	...	
South	1.04	(.97–1.12)	.2294	NA	...	
West	1.05	(.98–1.13)	.1420	NA	...	

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; PrEP, pre-exposure prophylaxis; Ref, reference.

^aAdjusted HRs were generated from multivariable Cox proportional hazard models. The commercial model was adjusted for age, sex, urban or rural location, and region; the Medicaid model was adjusted for age, sex, and race/ethnicity.

^bOther includes 8 Hispanic persons.

than half of PrEP users persisted for a year, with women and younger persons persisting with PrEP the shortest time [25]. While there are currently few data available to understand the reasons for these persistence differences, several factors have been proposed, including HIV or PrEP-specific stigma, less access to healthcare, financial constraints, or less support to persist with PrEP by their community or healthcare provider [26]. Although some of the social and system-level barriers might be not easy to overcome, the US Preventive Services Task Force has recently recommended PrEP and given it an A grade [4]. The A grade will require most public and private insurers to include PrEP services as a benefit with no deductible or copay, making PrEP more financially accessible, which may improve PrEP persistence for some.

HIV infections occur at a disproportionately high rate among young adults. More than 60% of infections diagnosed in 2017 were among persons aged 20–29 years [27]. Our study finding that younger persons persisted with PrEP for less time than older persons is consistent with other studies. Many studies have found that young age is associated with less adherence and persistence in taking daily medications regardless of the condition [28]. In an open-label study of PrEP use by young MSM aged 18–22 years, similar to our findings, only a third of study participants persisted with PrEP for longer than 1 year [29].

Especially for younger persons, low PrEP persistence might be associated with lack of access to healthcare or insurance coverage, or lack of perceived HIV risk [30, 31]. Our study population included only persons with health insurance, so some young PrEP users in our cohorts probably discontinued it for reasons other than lack of insurance. Given the high HIV incidence and low rates of PrEP adherence and persistence reported among young persons, interventions can be developed to support their PrEP persistence. Younger PrEP users might require more frequent provider visits and more intensive adherence and persistence counseling than older PrEP users. Nondaily PrEP, such as injectable long-acting PrEP drug or implants that will likely become available within a few years might be good options for young persons who have ongoing risk behaviors but difficulty taking a daily pill [32].

In 2017, 19% of HIV diagnoses were among women [27]. Despite an estimated 176 670 women who have indications for PrEP in the United States [5], only 2% have been prescribed PrEP [6]. Our findings suggest that women persisted for a shorter period of time compared to men. Several barriers to PrEP use by women have been identified [33], including low HIV risk perception [34, 35]. Some women might have used PrEP to safely conceive a pregnancy with an HIV-positive partner and discontinued it after becoming pregnant, resulting

in shorter periods of PrEP persistence [21, 36]. We found that commercially insured women of reproductive age persisted with PrEP for significantly less time compared to older women. Additional research is needed to explore the relationship between pregnancy and PrEP use.

The number of PrEP users with Medicaid included in the analysis was relatively small compared to the number of users with commercial health insurance; nevertheless, the Medicaid data allowed us to examine the difference in PrEP persistence by race/ethnicity. Our study found that black race/ethnicity was associated with shorter PrEP persistence compared to white or other race/ethnicity. While the bivariate association between lower persistence and black race/ethnicity was statistically significant, the association was not significant in the multivariable model after adjusting for other covariates. This might be due to the small sample size of PrEP users with Medicaid in our study. The black population has had disproportionately higher rates of HIV diagnoses relative to their representation in the US population. PrEP has been underutilized among at-risk black persons [6, 26]. The social and financial barriers that resulted in nonpersistence in PrEP among persons in the black population might be similar to those that prevent them from initiating PrEP [13]. Interventions are needed to reduce racial/ethnic disparities in PrEP uptake and persistence among black individuals.

Our study has some limitations. First, behavioral data were not available in the databases we analyzed, and we were not able to assess reasons for PrEP nonpersistence or discontinuation. Persons who initiated PrEP might have stopped using it for various reasons, such as a change in risk behavior, no longer with an HIV-positive partner, perceiving oneself as being at low risk for HIV, or having a significant adverse effect from PrEP medication [26]. Second, our analyses measured persistence based on prescription fill records, but a person who persists in refilling prescriptions may not be adherent. Third, we might overestimate persistence on PrEP when restricting the study sample to those continuously enrolled in their health plans for at least 12 months. We might have excluded persons without job stability who are more likely to discontinue PrEP. Additionally, the MarketScan commercial database we used for the study oversampled persons with higher income, and might contribute to overestimation. Fourth, only a limited number of unidentified states were included in the MarketScan Medicaid database, so our estimates of PrEP persistence among persons with Medicaid insurance cannot be generalized to the entire US Medicaid population. Our findings also cannot be generalized to PrEP users who self-paid or received their medication from a PrEP Medication Assistance Program. Finally, we did not account for PrEP reinitiation in this study, which is common among young users [37, 38]. Future studies to incorporate reinitiation and analyze gaps between prescription episodes by patient factors could be useful.

One of the strategies of the federal Ending the HIV Epidemic initiative is to prevent at-risk persons from acquiring HIV infection, including the use of PrEP [1]. PrEP will only be effective in preventing new HIV infections if it is used adherently and persistently by persons who are at risk of acquiring HIV. We found that persons in populations with the highest rates of HIV diagnoses, including young persons and black persons, persisted with PrEP for shorter periods of time compared to persons in other populations. A better understanding of reasons for discontinuing PrEP will inform interventions to support PrEP use by persons with substantial risk of HIV acquisition. Targeted approaches with efforts specifically designed for women, younger persons, and persons of color are needed to address their barriers to persisting with PrEP.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent views of the Centers for Disease Control and Prevention.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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