UNIVERSITY OF CALIFORNIA SAN DIEGO

PrEP Utilization in the United States, A sub-study of the Triumph Project at UCSD

A Thesis submitted in partial satisfaction of the requirements
for the degree Master's Degree

in

Public Health

by

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2023

The Thesis of Hollie David is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2023

DEDICATION

The work of this thesis is firstly dedicated to my mother. Though she may have passed long before my entrance to higher education, the life lessons she taught me have helped push me through life with a passion for education and equity.

I would also like to dedicate this thesis to the LGBT youth of this country. Personal challenges of living your truth are compounded by systematic asperity, I dedicate this work with strength and pride for our community.

EPIGRAPH

We should indeed keep calm in the face of difference, and live our lives in a state of inclusion and wonder at the diversity of humanity. ~~

George Takei

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LIST OF ABBREVIATIONS

PrEP	Pre-Exposure Prophylaxis, taken to prevent HIV
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome, Stage 3 HIV
EHE	Ending the HIV Epidemic in the US Initiative
LGBTQIA+	Lesbian, Gay, Bisexual, Transgender, Intersex, Asexual and more
LGBT	Shortened Version of LGBTQIA+
PWID	Persons Who Inject Drugs
US	United States of America
CDC	Centers for Disease Control and Prevention
BIPOC	Black, Indigenous and Persons of Color

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Dr. Sanjay Mehta and Alan Wells as well as the rest of the Triumph Project team at University of California, San Diego for their support of this project.

Secondly, I would like to express my gratitude for committee members Dr. Anegla Bazzi and Dr. Gretchen Bandoli for their guidance in the development of this thesis. The committee as a whole including Dr. Mehta and Mr. Wells have been exceptionally helpful in the achievement of this goal.

I would also like to appreciate the support of my classmates, professors and community for their patience and feedback in the development of this project.

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PUBLICATIONS

David. June 2023. PrEP Utilization within the United States. 2023 Annual Research Meeting. Academy Health, Seattle, Washington.

David, Wells, Mehta, 2023, HIV Preventative Medicine and Health Disparities, A sub-study of The Triumph Project. Public Health Research Day 2023. University of California, San Diego, California.

David, Wu, Andreiu, Sladek, Weibel. 2022. An Analysis of Roter Interaction Scale Positive Affect Score Variation- Interpretation and Statistical Methods. Public Health Research Day 2022. University of California, San Diego, California.

ABSTRACT OF THE THESIS

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by

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Master of Public Health

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Professor Sanjay Mehta, Chair

Professor Angela Bazzi, Co-Chair

Background

HIV pre-exposure prophylaxis (PrEP) is a key to the United States' (US) Ending the HIV Epidemic plan. Investigating the United States holistically to assess PrEP with inclusion of state level variables including politics, socioeconomic average status of citizens and new HIV diagnoses addresses research gaps left by locale or risk-group targeted studies. This research aims to 1) evaluate PrEP utilization in jurisdictions with the highest HIV new diagnosis incidence, 2) determine PrEP correlation with new HIV diagnoses, income, geopolitical, race and/or geo-spatial factors as to satisfy gaps in literature examining the disparities in PrEP utilization on a national scale.

Methods

Analysis of 2012-2019 PrEP rates from AidsVu implementing linear mixed methods statistical modeling. Years 2020-2022 were not included in analysis due to potential influence of the COVID Pandemic. The dependent variable was county PrEP rate. Fixed effects were HIV diagnoses from AidsVu, state income from US Census data, percentage of black, indigenous and people of color (BIPOC) in state populations from US Census data and governor political affiliation from National Conference of State Legislatures. Random effects were regions and counties of the US. 50 US jurisdictions with highest new HIV diagnosis rates analyzed.

Results

For each 10,000 U.S. dollar increase in mean income, there was a significant increase in PrEP utilization by 66.4/100,000 persons (95%CI 58.6-74.3, $p<0.001$). Jurisdictions with higher HIV diagnosis rates have reduced PrEP utilization -2.73/100,000 for each new 1 diagnosis per

100,000 in the population (95%CI -3.71 – -1.80,p <0.001). For each increase of BIPOC by 1 percentile point, PrEP utilization decreased by a rate of -522.34 per 100,000 prescriptions (95%CI -958.4 – -134.8,p <0.05).

Conclusion

Findings suggest lower income, higher rates of HIV diagnoses, and higher proportion of BIPOC persons correlate to lower rates of PrEP use. Regional location and political party of state governors was not associated with PrEP uptake.Lower mean state income and higher rates of HIV diagnoses are associated with lower rates of PrEP uptake. A direct relationship between income and PrEP rates was determined as well as an inverse relationship between new diagnosis rates and PrEP rates. It is imperative to improve public health practice for there to be an increased implementation on provider education on PrEP and PrEP stigma. Furthermore, expanding telehealth access and prescribing authority to pharmacists may improve that capture of at-risk patients with improved PrEP uptake.

INTRODUCTION

Pre-exposure prophylaxis (PrEP) is used for the prevention of HIV acquisition. Oral medication options for PrEP include emtricitabine in combination with either tenofovir disoproxil fumarate or tenofovir alafenamide once daily to prevent HIV infection, with injectable options now available.(1) PrEP can be up to 99% effective at protecting against sexual HIV transmission. (2)

PrEP provision in the United States is not equitable between at risk groups. Patients who are Black or Latinx, transgender, women or PWID are least likely to achieve sustained PrEP care, yet these populations are the most at risk for new HIV infections. (3)(5) Patients of color are prescribed PrEP at lower rates when compared to their white counterparts (3)(6) . This healthcare injustice is not only fueled by provider bias but also systematic issues. (3)

Geographically, it is possible to locate what may be termed as 'PrEP deserts'. Locales in the United States with higher proportions of people of color, uninsured and impoverished often have fewer PrEP specialized clinics than locales heavily populated by rich, white and/or insured constituents.

Public health in combination with politics and policy are all important factors that determine the location and scale of HIV outbreaks. Since the inception of the epidemic, HIV has been politicized. (7) State governors within the United States are key stakeholders in the prevention and treatment of HIV. Within each governor's power is the ability to encourage or terminate preventative medicine practices and funding in the fight to End the HIV Epidemic. (8) Implementation of effective public health practices relies on progressive and compassionate leadership to improve health outcomes and improve preventative medicine practices, such as PrEP uptake, to better serve marginalized populations within the United States.

This project serves to investigate the 50 local US jurisdictions with the highest new diagnosis rates and determine if PrEP is being utilized effectively to reduce new diagnoses in these jurisdictions. Within this analysis, the rate of change in PrEP rates over time will be assessed by regional location within the United States to determine geographical significance and disparities. Additionally, socioeconomic data by region will be used to determine regional wealth pattern correlation to PrEP rates. Gubernatorial election results by state will be analyzed for their effect on differential PrEP rates and used as a proxy for state government political affiliation. Distribution of BIPOC patients will be included in the analysis to determine racial disparities.

Analysis of PrEP utilization over time will be evaluated using a linear mixed methods model. Thus mixed methods were used to analyze data of repeated measures of groups over time. Mixed methods can account for random, or grouping effects of counties as well as fixed effects which are steady among counties. Fixed effects in a linear mixed methods model operate similar to effects, which are fixed, in a linear model. Random, or grouping effects, are integrated in linear mixed methods to represent hierarchical grouping. For the components of this study, random effects will be constituted as locales. Within such, a nesting effect of counties within states within regions or counties within regions will be implemented. PrEP measurements will be a fixed effect because we expect that there is an average relationship between PrEP measurements and time that will turn up again if we conduct the same experiment with a different sample of participants and items. Data for this analysis was acquired from AidsVu, US Census Data, and the National Conference of State Legislatures. (9)(10)(11) Quantitative analysis was performed using R version 4.0.3 (2020-10-10).

Literature Review

Pre-exposure prophylaxis oral medications reduce a patient's likelihood of contracting HIV from sexual contact and/or injection drug usage. Entricitabine in combination with either tenofovir disoproxil or tenofovir alafenamide are the current FDA-approved oral PrEP medications. Entricitabine in combination with tenofovir alafenamide is prescribed to prevent HIV from sexual interactions as well as protect persons who inject drugs (PWID), but not assigned female sex at birth. (12) Entricitabine in combination with tenofovir disoproxil is primarily prescribed to patients who were assigned female or male sex at birth who are at risk of contracting HIV from sexual interactions. Studies have identified various barriers to accessing and maintaining PrEP (13)(14)(15) . However, few studies have examined the disparities in PrEP access by county in the country and the degree to which economic and political differences between regions may account for differences in PrEP uptake and adherence.

This literature review serves to illustrate known barriers and disparities in pre-exposure prophylaxis for HIV throughout the United States.

It has been established in literature and will be examined further in this review, that there are differential PrEP rates by location in the United States. Furthermore, the following thesis analysis which this theoretical framework addresses to satisfy certain gaps in the literature includes not only examining the geographical disparities in PrEP utilization but also the impact of regional income rates and political affiliations of state leaders. Implementing income and political affiliations will serve as proxies to social determinants of health.

For the purpose of this review, a few acronyms will be used. HIV refers to human immunodeficiency virus and includes the later stage of the disease, AIDS or acquired immune deficiency syndrome. PrEP, as mentioned, refers to pre-exposure prophylaxis for HIV. PWID refers to persons who inject drugs. (16)

This review serves to critically examine existing literature regarding PrEP use in the United States over time as impacted by geographical location and other social determinants of health such as income level. The following review examines the availability of information on geographically related disparities for studying the association between PrEP uptake and social determinants of health.

This is a literature review conducted in October through November 2022 using Pubmed and Google Scholar internet search engines. For inclusion in this review, articles must have been published between 2012-2022 for time relevance. Publications must also be fully available online including author names, titles, publication sponsors and sources. Furthermore, this literature review only includes scientific papers which were published in English. Search terms for this review included "prep, state, stigma & HIV".

A total of 34 papers were included in the systematic review. Fifteen articles were excluded due to lack of relevance or duplication. Three articles were excluded due to lack of access as the full text of these papers was not publicly available. One paper was excluded due to being published outside of the desired timeline in June of 2011. Overall, twelve articles which met inclusion criteria are examined in this review.

Pre-exposure prophylaxis (PrEP) is prescription medication in the United States for prevention of HIV in high risk populations. PrEP is administered with the use of antiretroviral medications before HIV exposure (17). High risk populations who may qualify for pre-exposure prophylaxis medications include but may not be limited to: adult men who have sex with men, people who use injection drugs and people who regularly have sex without condoms without knowing their partner's HIV status. (18) Ending the HIV Epidemic created by the United States federal government supports PrEP as the key HIV prevention method. Increasing utilization of

PrEP by 40% in certain groups has the potential to reduce the new diagnosis incidence within said groups by up to one third. (13)

Disparities within PrEP care are not only linked to race but also socioeconomic status, gender, geography and sexual orientation. Stigmatizations such as racism, homophobia, classism and bias against PWID perpetuate low PrEP uptake rates within the United States. (22) Stigmatization within healthcare not only decreases positive health outcomes from PrEP but also fuels the cycle of systematic bias. When stratifying by race, PrEP rates are discordant with new HIV diagnoses. (23) At the time of PrEP's initial approval by the FDA, it was unclear as to how many adolescents and youths would be able to access the medication. Even today, the ability for an adolescent to consent for the medication without parental approval varies by state (24) (25) Furthermore, gender disparities in PrEP uptake are increasing as more women are diagnosed with HIV without adequate and equitable access to the preventative medication across the United States.(20)

Impediments to PrEP in the United States are financial as well as geographical on top of social barriers. The cost of PrEP for an individual within one calendar year can range from $8,000 to $14,000. It should be restated at this point that PrEP is intended to be implemented within populations with high risk and individuals who are HIV negative at the start of PrEP treatment. (27) Compounding bias in PrEP care is the fact that states within the Southern Region of the United States have the highest proportions of uninsured persons in their population. (26) Access to PrEP based on status of insurance, private or publicly funded, may further compound access to PrEP uptake throughout the country.(28)

With the current state of PrEP in the United States, including the need for growth in research and uptake, technology guided 21st century public health campaigns can be used to

increase awareness about HIV, PrEP and associated risk factors. The utility of social media, digital outreach platforms and targeted marketing to increase PrEP and overall HIV awareness are novel modes to be implemented and explored. For example, implementation of public health movements and projects can utilize internet media/news coverage to increase awareness about PrEP in suburban and urban areas of the United States.

The vast increase in remote access to prescribing providers and drug delivery systems could not only improve outcomes of campaign targets but also reduce overall HIV new diagnosis incidence. Utilization of telehealth could greatly increase PrEP uptake while improving outcomes of the Ending the Epidemic Campaign. Telehealth use can be differential in use by income and insurance status, (28) Programs such as Gay City in Seattle, Washington and PrEPIOWA in the state of IOWA have shown success in allocating public funding to telehealth PrEP services and can be used as a template for new and expanded programs. (29) An issue to be noted with the use of technological tools for increasing awareness is that it may further marginalize highly at-risk populations in rural areas, such as in the South or Midwest, with little access to the internet. (28)

Overall, differential PrEP rates throughout the United States are driven by social, financial and politically disparaging forces. The Ending the Epidemic campaign from the CDC, and other related campaigns such as the Triumph Project at UCSD work to reduce HIV incidence and thereby mitigate bias in HIV care. Further exploration of the highest need areas of the country is necessary to determine a systematic approach to increasing PrEP uptake and reduce HIV incidence. The following analysis will explore locales within the United States and the associations of regional financial status, state governance and time on PrEP rates.

CHAPTER 1

Methods

A. Statistical Methods

A mixed methods, repeated measures of time study was conducted on the Top 50 Jurisdictions based on new HIV diagnosis incidence between the years 2012-2019. Methods were based on a linear regression model predicting change in prep utilization of jurisdictions. Effect indicators of the economic, political, new diagnosis incidence and location of the jurisdiction during the years observed were studied.

Linear mixed methods were used to analyze data of repeated measures time series. PrEP measurements were a fixed effect as it is expected that there is an average relationship between PrEP measurements and time that will turn up again if we conduct the same experiment with a different sample of participants and items. (Brown, 2021) By implementing a linear mixed model, it is possible to determine the random intercept of County within Region as a nested random effect. Simultaneously, it is possible to account for the individual effects from fixed population level variables such as Income within the repeated measures experiment. Individual variables within counties had random intercepts while

To expand this approach, we will account for racial demographics, mean income, gubernatorial political associations, region and HIV incidence within jurisdictions of study. Fit of the model is based on observed data including years 2012-2019 within the study compared to expected outcomes. "South" was established as the reference level for Region, Right/Republican was established as the reference level for governor.

B. Setting and Subjects

CDC's Ending the Epidemic top 50 jurisdictions, which account for over half of new

HIV diagnoses, were chosen for analysis. Public health data were abstracted from AidsVu (31); income and race data from the US Census Bureau American Community Survey; gubernatorial election results from the National Conference of State Legislatures. (32) (33) PrEP and HIV new diagnosis data were provided by Symphony health through AidsVu. (31)

C. Study Analysis Protocol

Univariate analysis was applied to each fixed effect predictor to display significance of predictors without interactions. Null model was generated without any fixed effects to show significance of random effects. REML was set to false to account for the later use of AIC and due to the fact that there was a hierarchical structure within the random effect, termed nested random effects. Furthermore, the comparison of models and respective fixed effects structure necessitated the implementation of REML=F. (34)

Univariate selection and model ranking

Akaike information criterion (AIC) is a method used to determine the error prediction and superior model fit model during the selection process. (35) AIC can be applied to nested models such as the models of this analysis with nested random effects as well as non-nested models. Lower AIC correlates to the best fitting model but however does not encompass true reality as all mathematical models are derived from samples of the real world. Models with lower AIC's can be said to have the least loss of information in comparison to the truth of reality.

Multivariate selection and model ranking

Three models were generated using income, incidence, region, proportion of BIPOC population and party of governor as fixed effects. The model tot1_lmer accounts for no interactions of fixed effect. The full1_lmer accounts for fixed effects including interaction effect measure modification is accounted for here. The fullest1_lmer model incorporated both

independent and interactive fixed effects.

Multivariate models were implemented to describe fixed effects with interactions, fixed effects without interaction, and the overall fullest model including fixed effects accounting for with and without interactions. Interactions of fixed effects were analyzed to determine if conditional change to one predictor was correlated with the change of other relative fixed effects within the model. Random effects of the model were implemented to account for the violation of the independence assumption. To account for within-groups variance comparing between-groups for the repeated measures, random effects accounting for County nested within Region and Region alone were accounted for. (36)

As in the univariate analysis, AIC was again used to assess the most optimal model. In this initial post-hoc analysis, AIC was comparatively higher in the tot1_lmer model. Secondary analysis of the full1_lmer interaction model and fullest1_lmer model using anova() further showed no difference in model performance.

Variance inflation factor (VIF) is used as a check for multicollinearity which occurs when two or more predictors are correlated with each other. VIF of 1 is a perfect score with no collinearity between predictors, moderate score of 1-5 may not be need for concerned, 5-10 VIF can cause coefficients and p-values to be unreliable, VIF scores over 10 show faulty models that need to be restructured. (37) All three models were run through VIF and confirmed the use of the tot_lmer as the most optimal model.

CHAPTER 2

Results

Rates of PrEP utilization ranged from 2/100,000 to 674/100,000 persons. Figure 1 depicts the change in PrEP utilization during the duration of years of study stratified by region.

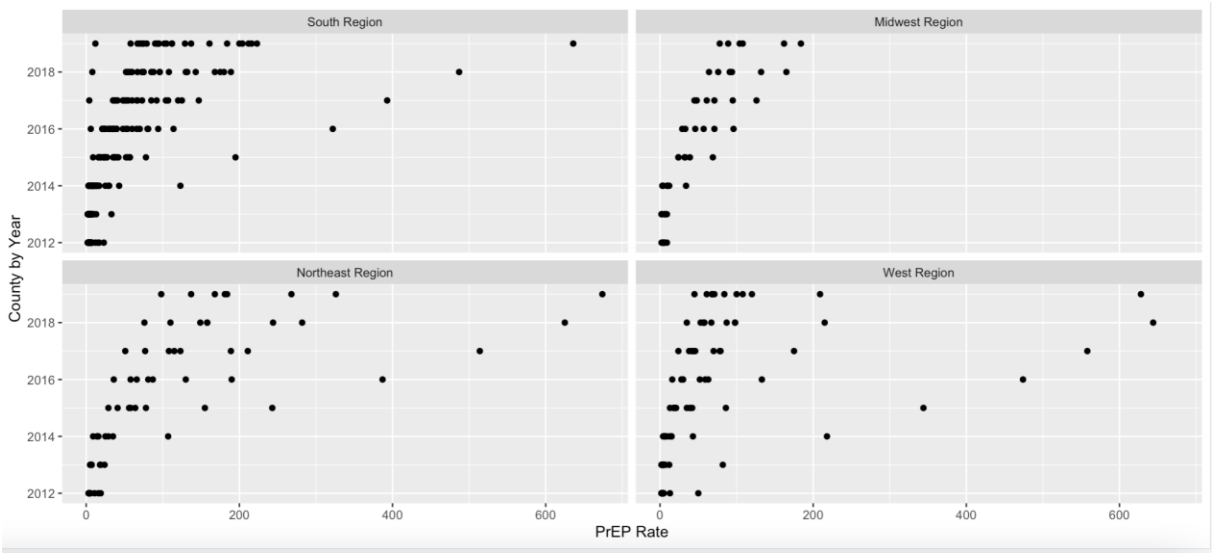

Figure 1. PrEP Rates by County, Stratified by Region. 2012-2019.

Income, Incidence, Region, and proportion of BIPOC population were found to be statistically significant in the univariate model selection process based on p-value << 0.05 as well as lowest AIC. AIC for all models showed the univariate model for income to be the most optimal in univariate analysis. In rank of lowest to highest AIC: inc_lmer model (4463.339), dx_mer model (4661.062), race_lmer model (4706.285), gov_lmer model (4721.639), no_fix_lmer model (4722.195) and reg_lmer model (4723.514). AIC for all models showed the univariate model for income to be the most optimal in univariate analysis. Due to potential over correction of the relationship between income and the random effect of Region:County, all other fixed effects will be included for further analysis.

Table 1. AIC scores implanted for model comparison.

	df	AIC
tot1_lmer	11	4430.80942032213
full1_lmer	29	4194.33363278629
fullest1_lmer	29	4194.33363278629

The AIC's shown in Table 1 show that the multivariate model without interaction terms slightly over-corrected the fit of the data in comparison to the models with inflation terms. AIC results of the multivariate model in rank from lowest (most optimal) to highest: full_lmer (4194.334), fullest_lmer (4194.334) and tot_lmer (4430.809) . Anova comparison of the full_lmer and fullest_lmer showed no difference in model performance. However, variance inflation factors during model comparisons were highly variable dependent on the interaction terms, as is depicted in Figures 2-4. VIF scores for the tot1_lmer model with no interaction terms ranged from 1.022-1.318. VIF scores for the full1_lmer model with interaction terms and fullest1_lmer model with both additive and interactive fixed effects were identical, ranging from 1.709-11.004. Due to the fatal model dynamics depicted by the VIF analysis, the 'tot' model with no fixed effect interaction terms was selected for final analysis.

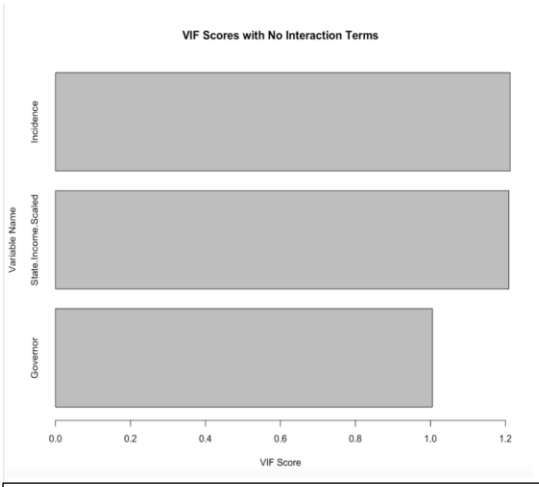

Figure 2. Variance inflation factor of model with no interaction effects.

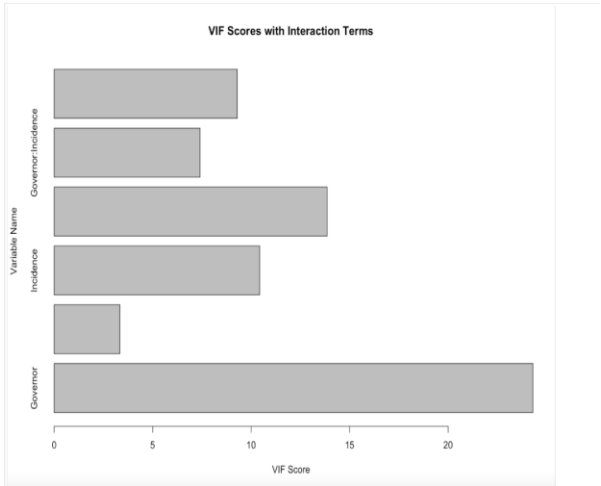

Figure 3. Variance inflation factor of model with interaction effects.

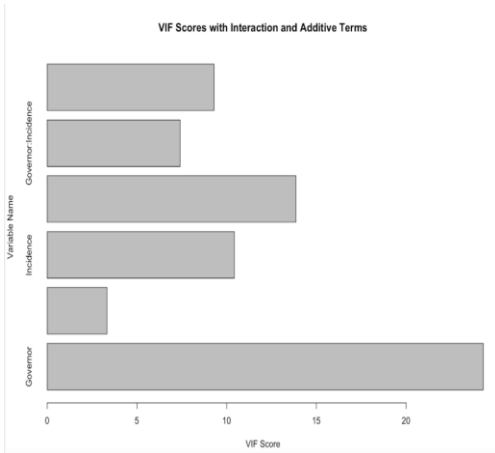

Figure 4. Variance inflation factor of model with additive and interaction effects.

Final multivariate results are described in Table 2. For each 10,000 U.S. dollar increase in mean income, there was a significant increase in PrEP utilization by 66.43/100,000 persons (95%CI 58.79-74.08, p<0.001). Jurisdictions with higher HIV diagnosis rates were associated with a decrease in PrEP utilization-2.74/100,000 for each new 1 diagnosis per 100,000 in the population (95%CI -3.63 – -1.84,p <0.001). A higher proportion of BIPOC population was associated with a significant decrease in PrEP rates by -522.34/100,000 (95%CI -903.72- -140.97, p < 0.05). Region was not significant for Midwest and Northeast locales. Note, the South was programmed as the reference Region for analysis. Comparatively, location within the West Region was found to be statistically significant with PrEP rate decrease compared to the South by -104.68/100,000 (95% CI -183.47 - -25.9). Variance in the model was accounted for by both fixed and random effect, establishing a good model fit for the data. Comparably, the marginal R-squared value, accounting for only fixed effects is 0.456 and conditional R-squared is 0.909.

Table 2. Results summary of final multivariate model

	County.PrEP.Rate		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-191.77	-315.95 – -67.58	**0.003**
Governor [Left]	-5.77	-24.91 – 13.37	0.554
State Income Scaled	66.43	58.79 – 74.08	**<0.001**
Incidence	-2.74	-3.63 – -1.84	**<0.001**
non white	-522.34	-903.72 – -140.97	**0.007**
Region [Midwest Region]	-74.80	-181.96 – 32.36	0.171
Region [Northeast Region]	-66.05	-154.35 – 22.25	0.142
Region [West Region]	-104.68	-183.47 – -25.90	**0.009**
Random Effects			
σ^2	2252.87		
$\tau_{00\ Region:County}$	11263.33		
ICC	0.83		
N_{Region}	4		
N_{County}	49		
Observations	400		
Marginal R^2 / Conditional R^2	0.456 / 0.909		

CHAPTER 3

Discussion

The objective of this study was to analyze pre-exposure prophylaxis, PrEP, uptake within the United States. The 50 jurisdictions within the United States with the highest HIV new diagnosis incidence were evaluated to determine if PrEP prescription uptake was correlated to new HIV diagnoses, mean income, gubernatorial election results and location. Approaching the data nation-wide in the United States for the assessment of pre-exposure prophylaxis for HIV with inclusion of state level variables including politics, socioeconomic average status of citizens and new HIV diagnoses is novel and holistic. In such, the approach was aimed to determine systematic barriers to a wider demographic of the population in comparison to more specialized studies.

This study has some limitations. Only years 2012-2019 were included in the analysis. Inclusion of more recent years 2020-2022 may be more telling of the state of affairs currently. Furthermore, for the purpose of this project, government influence is only relative to the executive branch within each state without regard to the legislative or judicial branches of the jurisdictions assessed. Another key limitation to this study is that other Ending the HIV epidemic data points such as linkage to care or viral suppression are not addressed, these values were accounted for by proxy within the new HIV diagnosis rates.

A strength of this study is the use of a linear mixed method regression over the classical linear regression. By implementing a mixed methods model, it was possible to account for the grouping effect of Regions as well as Counties by establishing random intercepts for each group. Furthermore, this is a novel analysis within the 50 jurisdictions defined by the Ending the

Epidemic Project of the CDC. As of know to the author, there is no known published article analyzing the combination of specific random and fixed effects across the United States. Future work on this analysis may include implementing more demographic information (including race and age) as well as the inclusion of more EHE predictor values (such as viral suppression rates and linkage to care).

Lower mean state income and higher rates of HIV diagnoses are associated with lower rates of PrEP uptake. A direct relationship between income and PrEP rates was determined as well as an inverse relationship between new diagnosis rates and PrEP rates.
These results support previous literature demonstrating socioeconomic disparities in PrEP utilization across the US. This supports empirical evidence of the impact of personal income proportional to health expenditures. (38) The inverse relationship between PrEP rates and HIV diagnosis rates may be expected as an indicator of inadequate access to HIV preventative medicine. Potential barriers to PrEP access may include provider bias, perceived lack of risk, and lack of access to medical providers or financial support including transportation costs. (39) Geospatial analysis displayed a differential in prescription counts between regions. Cost of transportation as well as clinic deserts may be attributing factors. (40) Lack of awareness (41) and stigma (42) may also hinder PrEP uptake overall. PrEP stigma can affect not only uptake of new patients but the adherence to medication schedules by persons already on PrEP. (43) Race was also associated with decreased PrEP utilization. Homophobic and racist stigmas are barriers to HIV-related medical services. Such stigmas can both be categorized as expected or experienced, as well as both expected and experienced. Fear, mistrust and shame are emotions

which may hinder PrEP uptake in high risk populations, particularly men of color who have sex with men. (44)

Implementing protocol to integrate pre-exposure prophylaxis patient education regardless of sexual or gender identity may improve the capture of at-risk patients. Patients with insurance are approximately four times as likely to receive PrEP. (45) Within patient health education, the emphasis must be made that PrEP is most often free of charge with Medicaid and private insurances. (46)

PrEP utilization is differential by race, mean income level and location throughout the US. Access to HIV preventative medicine is not equal between groups and particularly lacking within high risk groups, perpetuating the HIV epidemic. Larger education of providers to thus increase patient knowledge may assist in PrEP uptake. Inclusion of cost-effectiveness and destruction of stigmas can improve uptake while gathering a more representative patient population of those at risk for HIV on PrEP. Adequate HIV preventative medicine is key to terminating the epidemic. Systematic lack of PrEP utilization in high risk populations such as BIPOC, low socioeconomic status and persons living areas with high new diagnosis prevalence, patients are not adequately protected against HIV.

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