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Impact of Pre-exposure Prophylaxis (PrEP) on sexually transmitted infection (STI) incidence among men who have sex with men (MSM) in Mecklenburg County North Carolina

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Abstract Cover Page

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By

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BSPH
University of North Carolina Charlotte
2016

Vijaya Kancherla, PhD

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
2019

Abstract

Impact of Pre-exposure Prophylaxis (PrEP) on sexually transmitted infection (STI) incidence among men who have sex with men (MSM) in Mecklenburg County North Carolina

By Isaiah Omerhi

Objective: This study aims to determine whether MSM who were prescribed Truvada pre-exposure prophylaxis (PrEP) have a higher incidence of sexually transmitted infections (STIs) than MSM not using Truvada PrEP.

Design: Primary analysis of longitudinal STI data obtained from MSM attending Rosedale Medical and Amity Medical Group in Charlotte North Carolina, USA, and January 2016–October 2018.

Methods: Men who have sex with men (MSM) patients were identified and grouped into two, those who were prescribed Truvada PrEP and a second group not using PrEP (propensity score was used to match similar patients). Patients' STI data was used to compare the incidence of chlamydia, gonorrhea, and syphilis, and time to first symptomatic STI among PrEP users and nonusers.

Results: Ninety-eight Truvada PrEP users propensity score matched nonusers were included in the analysis. Incidence rate ratios (IRRs) for chlamydia, gonorrhea and early syphilis were 3.2 [95% confidence interval (95% CI): 1.9–5.3], 2.8 (95% CI: 1.7–4.6) and2.9 (95%CI: 1.5 – 5.6), respectively, comparing PrEP users to nonusers. Time to first symptomatic STI was shorter among PrEP users (120 days, 95% CI: 77 – 171) than among nonusers (185 days, 95% CI: 163–256).

Conclusion: Among MSM on Truvada PrEP, we observed a higher incidence of STIs and faster time to first symptomatic STI than MSM, not on Truvada PrEP. Truvada PrEP nonusers had a higher incidence of syphilis compared to Truvada PrEP users. However, there is insufficient evidence that PrEP maybe a contributing factor in increasing STI rates among MSM

Cover Page

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Background

Pre-exposure prophylaxis (PrEP) is part of a comprehensive HIV prevention strategy that includes safer sex practices, such as consistent and correct condom use, regular HIV testing, and risk reduction counseling. As part of PrEP, HIV-uninfected individuals who are at high risk of HIV infection take anti-retroviral medication daily to decrease their chances of becoming infected with HIV if and when they are exposed to the virus. The pill (brand name Truvada™) contains two medicines (tenofovir and emtricitabine) that are often used in combination with other medicines to treat HIV. When someone is exposed to HIV through sex or injection drug use, these medications work by preventing the virus from establishing a permanent infection. When taken daily, PrEP is highly effective for preventing HIV. Studies have shown that PrEP reduces the risk of getting HIV from sex by about 99% when taken daily, including men who have sex with men (MSM). Among people who inject drugs, PrEP reduces the risk of getting HIV by at least 74% when taken daily. From 2014 to 2017, PrEP awareness among MSM in 20 urban areas increased from 60% to 90%, and PrEP use increased from 6% to 35%. PrEP use increased in almost all demographic subgroups but remains low among black and Hispanic MSM.[1]

By routinely testing patients for HIV, assessing HIV-negative patients for at-risk behaviors, and prescribing PrEP as needed, health care providers can play a critical role in ending the HIV epidemic. Increasing PrEP use is a principal strategy of the ending the HIV epidemic.[2] On July 16, 2012, the U.S. Food and Drug Administration (FDA) approved Truvada™ for PrEP in combination with safer sex practices to reduce the risk of sexually acquired HIV-infection in adults at high risk.[3] PrEP is much less effective if it is not taken consistently and as PrEP only protects against HIV, condoms are important for protection against

[1] (2019)
[2] (Finlayson et al., 2019)
[3] (2012)

other STDs. Condoms are also an important prevention strategy, especially if PrEP is not taken consistently.[4] Truvada™ for PrEP is being approved with a Risk Evaluation and Mitigation Strategy (REMS) to minimize the risk to uninfected individuals of acquiring HIV infection and to reduce the risk of development of resistant HIV-1 variants. The central component of this REMS is a training and education program to assist prescribers in counseling individuals who are taking or considering PrEP. The training and education program did not restrict the distribution of Truvada™ but provided information about the importance of adhering to the recommended dosing regimen and understanding the serious risks of becoming infected with HIV while taking Truvada™ for PrEP. This is an important aspect of PrEP that helps to support healthy sexual behaviors to prevent incidences of HIV and other likely STI while on PrEP.[5]

The incidence of chlamydia, gonorrhea, and syphilis has risen sharply among men in the United States and other industrialized countries, with syphilis being disproportionately high among the MSM population. This may be coincidental with increased frequency of unprotected anal sex: in San Francisco for example, increasing proportions of MSM reported condom-less anal sex in the preceding 12 months in the National Health Behavior Study during the 2005–2014 study period. Persons attending sexually transmitted disease clinics also reported increases in the number of recent male sex partners in the same period. The motivation for decreased condom use may include confidence that use of PrEP for prevention attenuates transmission risk or the belief that HIV is no longer a serious health concern.[6] In studies of PrEP involving MSM, high rates of incident STI among MSM is driven by increasing rates of condom-less sex which in the context of PrEP may be only a part of the explanation for such occurrence. STI increases among MSM antedated the PrEP era, including increasing rates among already HIV-infected MSM. By definition, PrEP users are generally individuals with substantial risk for STIs, as well as HIV. Moreover,

[4] (Finlayson et al., 2019)
[5] (2012)
[6] (Marrazzo, Dombrowski, & Mayer, 2018)

routine STI testing has been part of these PrEP studies, providing an opportunity for enhanced detection of asymptomatic infections.[7]

It is important to know that these trends, if they are widely representative, are not necessarily bad for STI control. Some models have suggested that more frequent screening among MSM using PrEP might over time drive down rates of STIs, assuming screening increases substantially and STIs are appropriately treated; there is also the possibility that more treatment of gonorrhea, for example, might promote the faster spread of antibiotic resistance. Admittedly, evidence from randomized controlled trials would be needed to study these scenarios. Many studies have been conducted to understand the association between PrEP and STI over the years; however, very few studies have been published that address the association between PrEP and STIs in a non-experimental setting such as a clinic. Furthermore, STIs are increasing in the United States at the same time as there is an increase in the awareness and utilization of biomedical advances in HIV treatment as prevention (TasP) and prevention (PrEP).[8] In the observed population of MSM, rates of reported new HIV infections have stabilized, and even declined in some areas. On the population level, the uptake of PrEP could contribute to increasing STI rates because the regular, quarterly STI screening recommended for all people on PrEP may increase detection of asymptomatic or recent infections.[9] PrEP protects against HIV infection but does not offer protection against STIs such as syphilis, chlamydia and gonorrhea. The growing concern is that MSM who use PrEP have been observed to come in for STI treatment more frequently than before the initiation of PrEP.[10]

Increased availability of urine testing, extragenital testing-rectal, and oral swabs has resulted in an increased number of MSM being tested for and diagnosed with a chlamydial infection. The rates of infections varied among different racial and ethnic minority populations including sub-populations such as

[7] (Barreiro, 2018)
[8] (Traeger et al., 2019)
[9] (Schillinger, 2018)
[10] (Barreiro, 2018)

MSM.[11] During 2015–2016, the rate of reported gonorrhea increased by 22.2% among men. The magnitude of the increase among men suggests either increased transmission or increased case ascertainment (e.g., through increased extra-genital screening) among MSM or both. During 2000–2016, the rise in the syphilis rate was primarily attributable to increased cases among men and, specifically, among MSM. In 2016, men accounted for almost 90% of all cases of syphilis. Of those male cases for whom sex of sex partner was known, 80.6% were MSM. Reported cases of syphilis continued to be characterized by a high rate of HIV co-infection, particularly among MSM.[12]

In 2016, 39,782 people were diagnosed with HIV infection in the United States. The annual number of new HIV diagnoses declined 5% from 2001 to 2015. HIV testing has remained stable or increased in recent years, thus decrease in diagnoses suggests a true decline in new infections. The decrease may be due to targeted HIV prevention efforts. However, progress has been uneven, and diagnoses have increased among a few groups. In Mecklenburg County, more than 6,600 persons are living with HIV infection and as many as 700 more may be infected but unaware of their status.[13]

An estimated 103,009 men who have sex with men (MSM) resided in North Carolina in 2013, representing 2.3% of the 4,503,084 MSM in the United States. Of the 3,536,017 adult men of North Carolina, 2.9% had had sex with another man in the past 5 years, which was less than the overall percentage of adult men in the United States who were MSM (3.9%). Most MSM in North Carolina resided in central counties of large metropolitan areas (38.8%). Among counties or county-equivalent areas in North Carolina, Mecklenburg County had the largest population of MSM at 20,920, representing 20.3% of all MSM in the state.[14] For adults and adolescents newly diagnosed with HIV in 2017, MSM accounted for 64.5% of all cases.

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[11] (Jones et al., 2019)
[12] (Patton et al., 2014)
[13] (Grey et al., 2016)
[14] (Grey et al., 2016)

The Mecklenburg County Health Department (MCPH) initiated a pilot program to provide PrEP for HIV prevention in March 2018. Although the PrEP program for individuals with high risk of contracting HIV has been in existence for some time there is very little coordinated effort in delivery of PrEP to those who need it the most in the county. As a result, surveillance efforts process focused on PrEP and STI trends in the county are needed. This is crucial to understand the trajectory of the impact of initiating PrEP and its relationship, if any, with STIs among MSM in the county since the extent of PrEP usage and practices in the county is unknown.[15] Truvada™ is provided free by the pharmaceutical manufacturer (Gilead) and the PrEP evaluation project monitors the PrEP program for patient enrollment rates, adherence, and new HIV infections while reporting STI diagnosis.[16] This data analysis on PrEP aims to compare the incidence rate of STIs among MSM who are Truvada PrEP users and nonusers in two clinics, Rosedale Medical and Amity Medical Group, in Mecklenburg County of North Carolina.

Method

Study Design, Setting, and Population

This is a primary data analysis of MSM who were prescribed PrEP from two clinics, Amity Medical Group and Rosedale Medical, both in Mecklenburg County of North Carolina, between January 2016 and October 2018. This analysis study is part of a Mecklenburg County PrEP Project of 2018. Clinicians from both clinics evaluate all patients for PrEP eligibility at routine visits, and those who meet the recommended criteria are offered PrEP through the clinic. AthenaNet is the electronic medical record (EMR) used to store and generate patient data for both clinics. This data includes identification of MSM on PrEP, which was extracted for this analysis. Patients who are on PrEP are tested for HIV and STIs at their initial visit and are given (prescribed) a 3-month prescription for PrEP. They return 1 month

[15] (Harihar, Witt, & Robinson, 2018)
[16] (Clasen-Kelly & Morgan, 2017)

after PrEP initiation, and then quarterly for clinical follow-up and monitoring, including HIV and STI testing. Included in this analysis are MSM who were prescribed PrEP, are HIV-negative, and have at least 12 months follow-up period in the dataset. Our comparison group (Truvada PrEP nonusers) was composed of HIV-negative MSM who attended both clinics between January 2016 and October 2018 period. Also, to be included in this analysis patients must be 18 years or older and those who were HIV positive on the first occasion (January 2016) were excluded from the analysis. The comparison group was propensity score-matched to PrEP users. The rationale for this approach was that PrEP is not widely accessible or affordable to a number of MSM in the county so the data will be best comparable to PrEP nonusers in both clinics when propensity score-matched patients to similar controls.[17] The main variable of interest for this study is the incidence of STIs among MSM who were prescribed PrEP compared to MSM PrEP nonusers for the same period. Other covariates that were considered and controlled for in this analysis include patients' age, race, marital status, education, alcohol use, and drug use.

Propensity Score Matching and Comparison Group Formation

Propensity score matching technique was used to select a group of comparison patients who were most similar to our PrEP users. These are MSM patients not on PrEP who present similarly as those on PrEP in both clinics at the same period of the investigation.[18] The goal of propensity score matching is to approximate the effect of randomization by balancing observed covariates between study groups.[19] Seven variables were included in the propensity score model, relating to STI diagnoses and demographic characteristics. Data for the propensity score model were from the initial PrEP visit for PrEP users and from the first clinic visit between January 2016 and October 2018 for PrEP nonusers.[20] Optimal fixed ratio

[17] (Scott & Klausner, 2016)
[18] (2018)
[19] (XU & Kalbfleisch, 2010)
[20] (Montaño et al., 2019)

matching 1:1 without replacement was used to select PrEP nonusers for each PrEP user based on their propensity scores.

Data Sources, Measures and Data Linkage

For both PrEP users and PrEP nonusers, we obtained data on demographics, clinic attendance, visit dates, PrEP status, and bacterial STI diagnoses from the clinic's EMR. Bacterial STIs obtained for this analysis were gonorrhea, chlamydia, and syphilis. These were not categorized based on the different types and stages; rather, any diagnoses of bacterial STI including gonorrhea, chlamydia, and syphilis was included in the analysis.[21]

Sexually Transmitted Infection Testing

PrEP patients attend an initial evaluation (baseline) visit and patients who are prescribed PrEP are required to return to the clinic for a 1-month follow up. After the 1-month visit patients are expected to make quarterly appointments for clinical follow-up and monitoring. MSM attending these clinics who were prescribed PrEP complete behavioral questionnaires for the intake process. Other MSM patients who are not prescribed PrEP go through the same intake process. Patients go through HIV and STI panel screening which includes testing for gonorrhea, chlamydia, and syphilis on initial clinic visits. Patients who are on PrEP are required to return to the clinic for their one-month STI screening after receiving the PrEP prescription and are also required to return quarterly after their first month for follow up visits. These quarterly visits involve HIV and STI screening.[22]

Statistical Analysis and Follow-up Time Calculation

Poisson regression was used to compare the incidence of bacterial STIs between PrEP users and PrEP nonusers. PrEP users were followed from their first PrEP prescription date for at least 12 months. Nonusers were also followed for the same period from the first clinic encounter date. During follow up

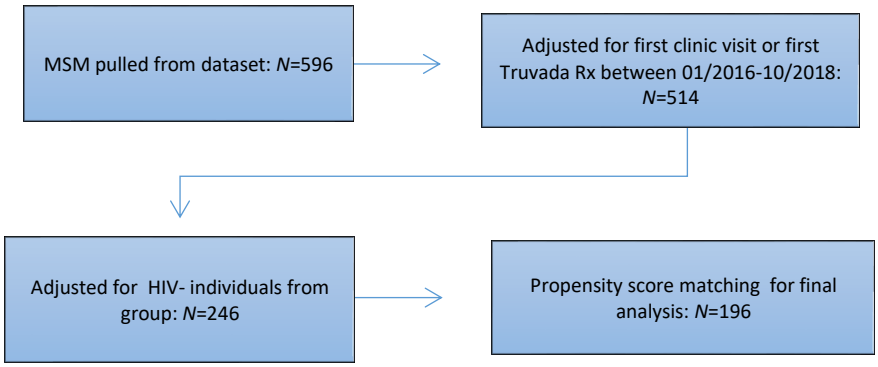
[21] (2019)
[22] (Saberi, Berrean, Thomas, Gandhi, & Scott, 2018)

period both PrEP users and PrEP nonusers diagnosed with chlamydia, gonorrhea or syphilis were counted as outcomes. To account for ascertainment bias resulting from more frequent STI screening among PrEP users, we compared time to first symptomatic STI between PrEP users and nonusers using Kaplan–Meier survival analysis, with follow-up time for both groups censored at the first diagnosis. We used a log-rank test to compare median time to first symptomatic STI between the groups. SAS 9.4 was used for all analysis and two-sided statistical tests were performed at a significance level of 0.05.[23]

Results

A total of 596 MSM patients from Amity Medical and Rosedale Medical clinic of in Charlotte, North Carolina was extracted from clinics' EMR. Using the initiation timeframe of January 2016 to October 2018 and an observation period of January 2016 to October 2019, 514 MSM patients who had a first clinic visit date or first PrEP prescription date were extracted. This number was further reduced to 246 when HIV-positive MSM were excluded from the analysis. PrEP users were propensity score matched for PrEP nonusers based on demographics, resulting in a comparison group of 196 patients (see Figure 1).

Figure 1: Patients included in analysis



[23] (Barreiro, 2018)

Among PrEP users, the median length of time contributed to the analysis is 1.65 years [interquartile range (IQR): 1.48-3.45]. Both study groups were balanced in terms of age, race/ethnicity and prior STI diagnosis. The mean age for the PrEP user groups was 35.7 years with a standard deviation of 11.3 years and the mean age for PrEP nonusers was 38.3 years with a standard deviation of 10.2 years. For both PrEP users and PrEP nonusers, the majority of the patients' ages were between 18-39 years. Half of both groups was non-Hispanic white. Of PrEP users, 10.2% had prior STI diagnosis, compared to 4.1% among Truvada nonusers (Table 1). Other variables including education, marital status, alcohol and drug use were not significant (p-value > 0.05).

Table 1. Baseline characteristics of MSM patients from Rosedale Medical and Amity Medical Group in Mecklenburg County 2016-2018 (N=196)

Variable	PrEP Nonusers		PrEP Users		*P* value
	n	%	n	%	
Age (Mean, SD)	38.2 (11.3)		35.7 (10.2)		0.1087
Race/Ethnicity					
Non-Hispanic Black	24	24.49	20	20.41	0.7821
Non-Hispanic White	50	51.02	49	50.00	
Hispanic any race	6	6.12	9	9.18	
Other	18	18.37	20	20.41	
Education					
High school diploma or less	46	46.94	48	48.98	0.7749
Post high school education	52	53.06	50	51.02	
Marital status					
Married	11	11.22	11	11.22	0.9859
Single	62	63.27	63	64.29	
Unknown	25	25.51	24	24.29	
Alcohol Use[a]	80	81.63	77	78.57	0.5914
Drug use[b]	18	18.37	17	17.35	0.8521
Prior STI Diagnosis[c]	4	4.08	10	10.20	0.0961

PrEP, pre-exposure prophylaxis; SD, standard deviation.

[a]Alcohol use: yes or no, only yes was reported.

[b]Drug use: yes or no, only yes was reported.

[c]Prior STI diagnosis: STI diagnosis prior to PrEP prescribed date for PrEP users and STI diagnosis for PrEP nonusers prior to clinic encounter date for analysis time frame.

Table 2 provides incidence of each STI, comparing PrEP users to PrEP nonusers. Among PrEP users, incidence of chlamydia, gonorrhea and syphilis was 24.2, 16.6 and 8.9 per 100 person-years, respectively. PrEP users had an approximately four-fold higher incidence rate than PrEP nonusers for chlamydia (IRR: 4.4; 95% CI: 2.2-8.6), and approximately two-fold higher incidence rate for gonorrhea (IRR: 2.3; 95% CI: 1.2–4.5). Syphilis on the other hand was approximately three-fold high for PrEP nonusers compared to PrEP users (IRR: 0.3; 95% CI: 0.1-0.8). The analysis found that during a mean follow-up of 1.3 years (3185 person-years), there were 2928 STIs diagnosed (1434 chlamydia, 1242 gonorrhea, 252 syphilis) among 1427 (48%) of the total participants. Overall, the STI incidence was 91.9 per 100-person-years, with 736 participants (25%) accounting for 2237 (76%) of all STIs. The median time to STI diagnosis for PrEP nonusers was 858.5 days [IQR 14-1383] and that of users was 698 days [IQR 41-1306]

Table 2: Incidence of STIs among PrEP users and nonusers attending Rosedale Medical and Amity Medical Group – Mecklenburg County (2016–2018), *N*=196

STI	PrEP nonusers (n=98) Incidence per 100 person-years	PrEP users (n=98) Incidence per 100 person-years	IRR[a]	95% CI
Chlamydia	5.5	24.2	4.4	2.2-8.6
Gonorrhea	7.0	16.6	2.3	1.2-4.5
Syphilis	8.6	2.6	0.3	0.1-0.8

IRR, incidence rate ratio; CI, confidence interval; PrEP, pre-exposure prophylaxis.
[a]Model for IRR are clustered by patient ID and the IRR for MSM in both Rosedale Medical and Amity Medical Group in Mecklenburg County North Carolina per year for the duration of the analysis period 2016 to 2018.
[b]Model was not adjusted for sub-categories of STI; all new STI cases within the analysis period were included.

The median time to chlamydia infection among PrEP nonusers was 984.5 days [147-1383] while among users it was 747.5 days [69-1306]. The median time to gonorrhea infection among PrEP nonusers was 984.5 days [14-1383] while among users it was 768.5 days [41-1306]. The median time to syphilis infection among PrEP nonusers was 925.5 days [15-1383] while among users it was 802.0 days [120-1306] (see Table 3).

Table 3: Time to STI among Truvada PrEP users and nonusers in Rosedale Medical and Amity Medical Group in Mecklenburg County North Carolina (2016-2018), *N*= 196

STI	PrEP nonusers (n=98)		PrEP users (n=98)		*p*-value
	Median time to event in days[a]	IQR in days	Median time to event in days[a]	IQR in days	
Chlamydia	984.5	147-1383	747.5	69-1306	<0.01
Gonorrhea	984.5	14-1383	768.0	41-1306	<0.01
Syphilis	925.5	15-1383	802.0	120-1306	<0.01

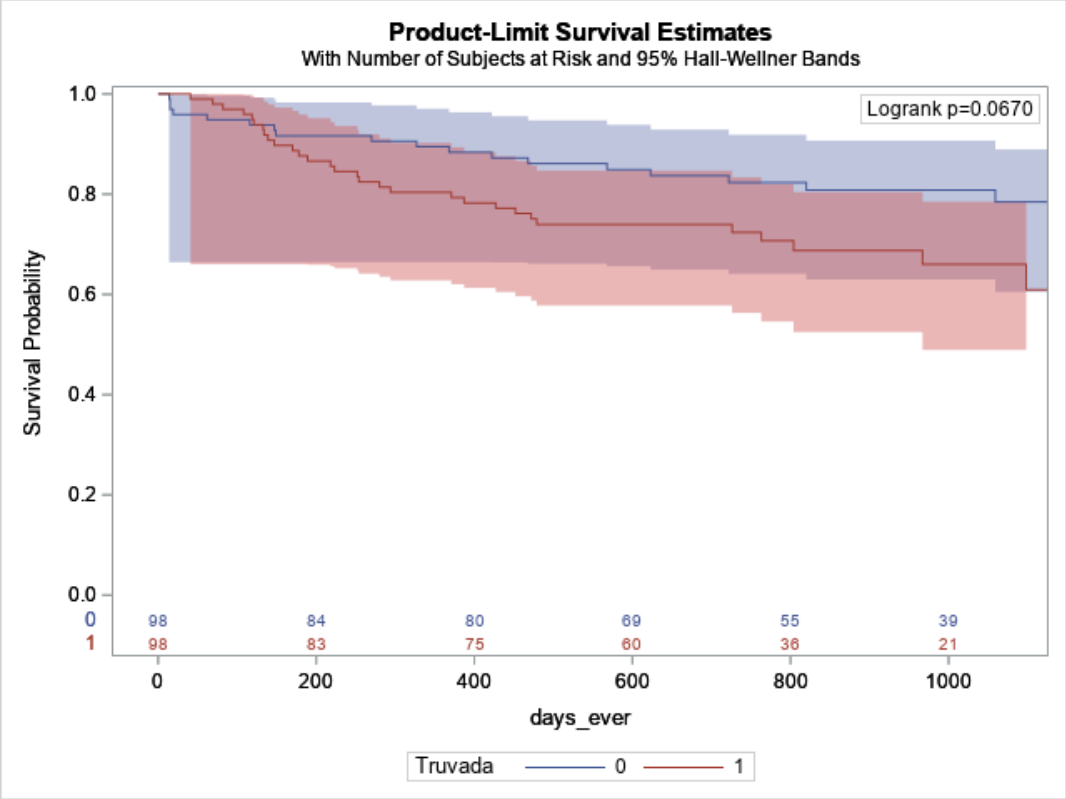
IQR, interquartile range; PrEP, pre exposure prophylaxis.
[a]Median time to event, median time to STI.

Discussion

Comparing MSM who are Truvada PrEP users to nonusers, the analysis indicates a four-fold higher incidence of chlamydia and two-fold higher incidence of gonorrhea. However, PrEP users were also 2.5 times more likely to have had a prior STI diagnosis at baseline than nonusers. The analysis also indicates that syphilis has a three-fold higher incidence rate for MSM PrEP nonusers compare to PrEP users. Broad increases in STI screening and detection are likely occurring independently of PrEP, due to increased availability of free testing opportunity around the county for MSM in general.[24]

[24] (Nguyen et al., 2018)

Figure 2: Kaplan-Meier of STI incidence between Truvada PrEP users and nonusers



Intersection; non-parallel curve violates PH assumption for the effect of PrEP between groups

When comparing the survival time for both groups, MSM PrEP users showed a higher STI survival probability compare to nonusers (see Figure 2). The result of the unadjusted effect of STI incidence (chlamydia, gonorrhea and syphilis) from Kaplan-Meier (KM) survival curve for this data indicate that MSM PrEP users have a better survival rate than MSM PrEP nonusers. As part of the PrEP program, regular HIV and STI testing is required and further findings suggest that PrEP use is associated with a higher risk of bacterial STIs incidence as a result of bias resulting from increased STI screening among PrEP users. Other reports from the county's health department have suggested increased incidence of syphilis among MSM. The independent t-test for chlamydia, gonorrhea and syphilis outcomes was significant for syphilis but not significant for chlamydia and gonorrhea. The KM curve indicates the proportion of MSM PrEP nonusers at risk at time t for STIs is larger than the proportion of MSM PrEP users before the point of intersection, an indication that PrEP may have played a role in the risk of STI among MSM PrEP users in

the first 120 days after PrEP use. However, after the intersection, PrEP use seems to have the opposite-protective effect.

This KM curve suggests a non-proportional hazard (PH). In this case, 'non-proportional' means that the effect of the independent variable (PrEP) is not constant over time. In other words, the hazard ratio is likely to change as time progresses. The regular proportional hazard Cox model does not accommodate such effects. One of the main assumptions is that the hazards are proportional. This difference could be due to the true hazards being non-proportional or the fact that there is a lot of variance in the tail estimates of the KM curves. Note that at this point the total group of 98 patients will have declined to a very small population still at risk. Both groups have patients experiencing the event and patients being censored. As the population at risk declines, the survival estimates become less certain. The 95% confidence intervals around the KM lines have increased width. This is important for the estimation of hazards as the population at risk and number of events in the final period of the analysis is low. Therefore, this period contributes less to the estimates in the initial Cox model. The effect of small numbers in the final period of the analysis is that the estimates of the hazards at those points in time are uncertain. Consequently, based on the unadjusted STI incidence it is less certain whether the apparent violation of the proportional hazards assumption is due to chance or the effect of the significant difference in the variance of syphilis incidence between groups. This suggests that the variance between groups for the incidence of syphilis modifies the effect of the unadjusted KM curve of the unadjusted STI incidence between the groups. Invariably the result from this analysis will not be controlling of the effect modification because the effect modifier variable syphilis is also an outcome variable for the analysis.

In recent studies, including two meta-analyses of STI incidence among PrEP users, reported incidence of STIs among PrEP users are in the range of 38.0– 56.7 per 100 person-years, 37.5–51.7 per 100 person years and 9.1–14.5 per 100 person-years for chlamydia, gonorrhea and syphilis, respectively. These results are further supported by incidence of chlamydia and gonorrhea among PrEP users obtained

from this analysis (24.2, 16.6 and 2.6 per 100 person-years, respectively) which were similar in proportion to this and other previous studies. However, unlike other studies, this analysis found that incidence of syphilis was much lower among Truvada PrEP users compare to nonusers.[25] Although the reported incidence of gonorrhea and chlamydia during Truvada PrEP use is somewhat similar to our group of MSM Truvada PrEP users, the incidence of syphilis was higher among Truvada PrEP nonusers compare to users. Indeed, the hypothesis that Truvada PrEP users would experience higher incidence and faster time to first symptomatic STI was supported by the results in this analysis, providing evidence that Truvada PrEP use is associated with an increased risk of STIs independent of increased screening frequency. However, this analysis did not find evidence that Truvada PrEP use can be linked to increased incidence of syphilis. More research is required to understand why the incidence of syphilis did not follow similar pattern as seen in other settings and documented reports.[26]

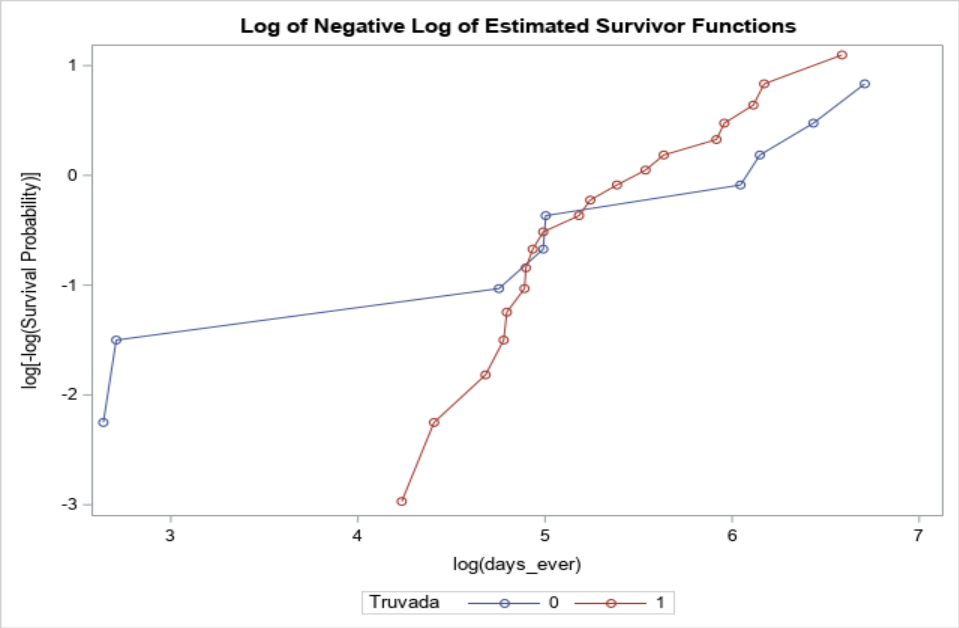
Individuals who have once tested positive for syphilis will always have a reactive positive result for subsequent syphilis testing even after a successful treatment of the infection. To avoid a situation where the data captures used in this analysis count every reactive positive syphilis test, leading to possible double counting, only new cases of initial positive syphilis infection were counted.[27] Possible reinfection of syphilis was also accounted for by reporting patients prescriptions associated with syphilis found in clinic encounter diagnosis records of patients.

The method used for this analysis addresses several concerns in the data analysis approach for PrEP use and STI risk research, including difficulty of comparison group formation, which has been a source of limitation present in many past studies. This analysis observed an increased STI risk among PrEP users relative to nonusers. Incidence of STIs among MSM has been increasing over the past decade

[25] (2017)
[26] (Jenness et al., 2017)
[27] (Henao-Martínez & Johnson, 2014)

in Mecklenburg County and nationally, and evidence that PrEP may be contributing to these increases is troubling. However, the findings of this analysis are not conclusive and do not negate the tremendous success of PrEP as a tool for HIV prevention[28].

Figure 3: Log-Negative Log of Estimated Survivor Functions of STI incedence among PrEP users and nonusers



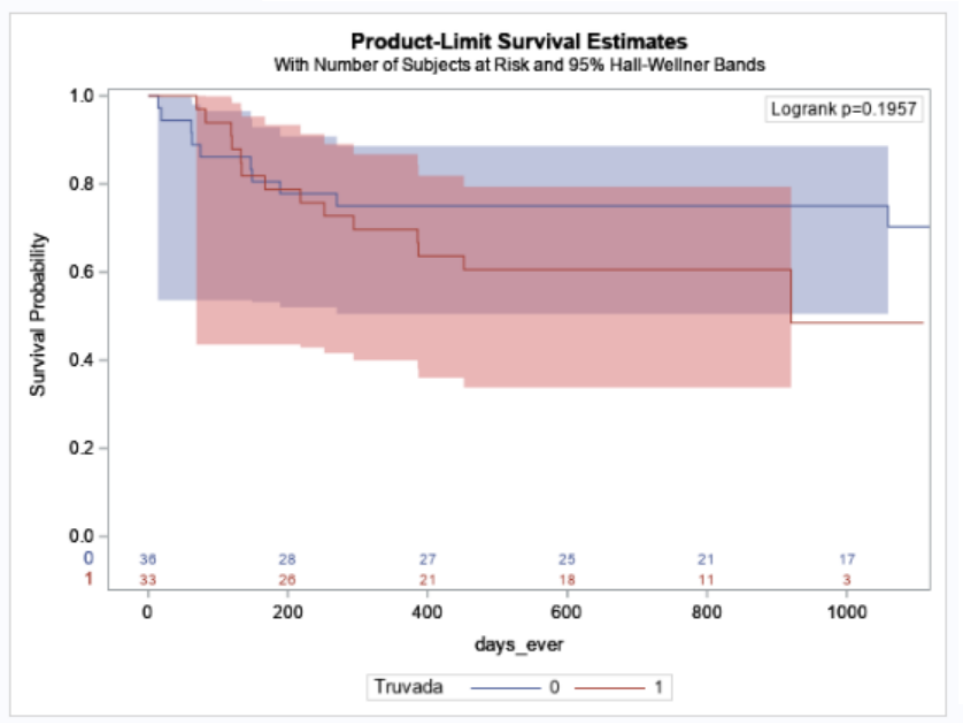
PH assumption violated

The survival curves are compared statistically to test the null hypothesis i.e. there is no significant difference regarding survival time to STI among the two groups. This null hypothesis is statistically tested using log-rank test and Cox proportion hazard test. The PH assumption is not satisfied because there is strong evidence of nonparallelism of the log-log curves. Further analysis was carried out to ascertain the difference in the incidence of STI if any by age category among PrEP users and nonusers. For this analysis, age was categorized as 18-29 years, 30-39 years and 40+ years based on the age distribution of PrEP users. The frequency of age distribution between both groups was similar among PrEP users and nonusers for 30-39 years category. Overall, the KM survival curve indicates an increase in STI incidence

[28] (Nguyen et al., 2018)

among PrEP users compare to nonusers over time. This is an interesting finding because this age category 30-39 years had fewer PrEP users than any of the other age categories and its log rank p is lower at 0.1957 than the other age categories.

Figure 4: Survival curve for PrEP users and nonusers in age category 30-39 years



Age category 30-39 years among PrEP users and nonusers
Other categories show slightly similar trend

Limitations

There are several limitations to this analysis. First, those who were prescribed PrEP in either clinic may not be representative of the wider population of MSM in the county. Hence, selection bias may be present in this analysis as individuals who use these clinics may have unique characteristics that were not accounted for in the analysis, such as the patient's address and type of insurance. Second, only clinical testing data were extracted and no data on STI treatments prescribed to participants were available; it is therefore not certain if every STI was treated effectively and if all positive diagnoses were incident infections. Third, though helpful in reducing within-group bias, propensity score matching assumes the

variables included in the propensity score can predict the likelihood of PrEP use, but this is inconclusive. Such an assumption may result in biased estimates of the impact of PrEP on STI risk if not properly accounted. There is a lack of available data on STI screening frequency for both groups and it was assumed that each time patients attend appointments in the clinics there is either an event or censoring, resulting in an analysis of the incidence of symptomatic STIs and comparison of time to first symptomatic STI. Fourth, there was inconsistent data entry by clinic staff members and this limits the quality of data available for a more robust analysis, which impacts the validity of the result to adequately respond to the research question. Therefore, our results should be interpreted with caution. Propensity score matching approximates the effect of randomization and allowed us to balance a large number of observed characteristics between study groups. Further, this method of comparison group formation enabled us to identify PrEP nonusers who were most likely to have been on PrEP, if it had been available.[29]

Conclusion

The result from the analysis showed that among MSM Truvada PrEP users, the incidence of the STIs gonorrhea and chlamydia was higher than compare to nonusers, but the incidence of syphilis was higher among PrEP nonusers compare to users. Overall, these findings emphasis the importance of frequent STI testing among MSM using PrEP. Also, the results from this analysis demonstrated that STI prevention campaigns should not focus solely on condom use but also on reducing the time to STI diagnosis and treatment by promoting easy access to frequent testing. The results highlight the importance of ongoing screening and treatment of STIs among PrEP users as an important component of PrEP patient care, and PrEP programs can be leveraged to continue to engage MSM in more comprehensive STI prevention programs in the future. The success of PrEP programs may provide a unique opportunity to

[29] (Calabrese, Earnshaw, Underhill, Hansen, & Dovidio, 2014)

design and implement novel interventions to address increasing STI rates in this population. In addition, the data entry process for these clinics needs attention, clinic workers and administrators involved in patient data entry from intake to follow-up must apply standardized data entry and data quality control techniques. This would allow for more accurate capture of detailed events over time and provide valuable information to predict trend and study relationship between PrEP and STIs.[30]

[30] (Harawa et al., 2017)

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