When Doesn't Clinical Efficacy Translate into Real-World Effectiveness? Evidence from PrEP

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Abstract

Why did the introduction of pre-exposure prophylaxis (PrEP), whose clinical trials demonstrate over 95% efficacy in preventing HIV, coincide with a plateau in diagnoses that ended decades of steady decline? This study draws on epidemiological, pharmaceutical, and Census data to estimate PrEP's real-world effectiveness and investigate why the drug failed to reduce population-level HIV transmission. To overcome selection bias in uptake, we exploit two facts: PrEP is used almost exclusively by men who have sex with men, and regional concentrations of male same-sex partnerships vary widely. Using a synthetic-control approach, we show that counties with higher same-sex partnership rates experienced greater PrEP uptake, which in turn, lowered transmission rates. Our findings indicate that 28 additional users avert one new diagnosis. Finally, while PrEP uptake is similar between Black and White men, eight-times greater incidence among Black men implies significant underutilization relative to need, diminishing the drug's real-world effectiveness.

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1 Introduction

Many medical interventions show considerable promise in experimental settings but fail to generate equivalent results in real-world contexts. The divergence between efficacy in clinical trials and effectiveness in real-world use — known as the efficacy-effectiveness gap — has been observed for range of interventions, including insecticide-treated bed nets (Ashraf et al., 2014; Hill et al., 2013) and diabetes therapies (Carls et al., 2017). Nowhere is this issue more salient than for pre-exposure prophylaxis (PrEP) for the prevention of Human Immunodeficiency Virus (HIV), where clinical success has struggled to translate into real-world impact. Approved by the U.S. Food and Drug Administration in 2012, PrEP was hailed as a transformative drug, with randomized controlled trials demonstrating over 95% efficacy in preventing HIV infection. Due to its high efficacy and safety profile, public health officials embraced PrEP as a "miracle drug" and an essential tool in ending the HIV epidemic (Fauci and Marston, 2015). Paradoxically, following the introduction of PrEP, HIV transmission rates in the U.S. began to plateau, ending a decades-long decline in infections.[1]

This study estimates PrEP's real-world effectiveness to investigate why HIV transmission rates leveled off after its introduction, drawing on epidemiological, pharmaceutical, and Census data from 2008 to 2022. This plateau is puzzling because, since HIV is an infectious disease, PrEP should protect not only those who use it but also non-users through reduced community-wide prevalence, increasing the drug's real-world effectiveness. Although clinical trials demonstrate that PrEP nearly eliminates the risk of HIV for users, several factors could lower its effectiveness in practice. Adverse behavioral responses, such as engaging in risky sexual practices due to moral hazard, could diminish its impact, particularly if changing norms lead to broader risk-taking in the unprotected population. Additionally, underutilization among the highest-risk populations could lower the drug's effectiveness.

Simulation studies based on clinical trial evidence projected that PrEP's introduction would sharply reduce HIV transmission (Supervie et al., 2011; Gomez et al., 2013). However, these projections rely on strong assumptions about behavioral responses to PrEP, such as its uptake and diffusion to at-risk populations. The observed plateau in new infections beginning in 2013 also contradicts the predictions of many such studies (see Figure 1). Empirical evidence of PrEP's causal impact on population-level transmission remains scarce.

The central challenge in estimating PrEP's real-world effectiveness is that users tend to

[1]This reversal is concerning given the remarkable progress achieved in the early 2000s through expanded testing, prevention efforts, and antiretroviral therapies to treat HIV. By 2013, new infections had stabilized at roughly 39,000 cases per year, which the Centers for Disease Control and Prevention (CDC) identified as a inflection point in the campaign to control the epidemic (CDC 2019).

be at higher baseline risk for infection, leading naïve ordinary least squares estimates to suggest that usage increases incidence. To overcome this selection bias, we take advantage of two facts: (i) PrEP is used almost exclusively by men who have sex with men (MSM), and (ii) MSM concentrations vary considerably across U.S. regions. Using a synthetic-control strategy, we compare counties with varying levels of Census-derived male same-sex partnership shares to estimate how expanded PrEP use affected transmission rates. This empirical strategy creates a synthetic counterpart for each county to adjust for confounders in HIV transmission, and then isolates variation in PrEP uptake driven solely by regional differences in male same-sex partnership concentrations. This paper aims to identify PrEP's real-world impact following its approval by the U.S. Food and Drug Administration, capturing mechanisms such as access, awareness, and behavioral responses, rather than measuring the drug's efficacy, which has been already established in clinical trials.

We begin by demonstrating that counties with higher rates of male same-sex partnerships experienced greater PrEP uptake. By 2022, counties in the 90th percentile of same-sex partnerships had usage rates four times greater than counties in the 10th percentile. Uptake is almost exclusively driven by MSM: while this population comprises 40% of those indicated for the drug, they represent 95% of users. Consequently, PrEP's introduction had a causal, negative impact on new infections among MSM: 28 additional users correspond to one averted HIV diagnosis in 2022. By contrast, we find no evidence of reductions in transmission among women or heterosexual men, populations for whom PrEP use is negligible. Finally, a battery of exercises using HIV testing data and CDC-derived incidence estimates confirms that PrEP's introduction led to a true decline in infections, rather than merely increasing detection of undiagnosed cases.

Why, then, did the introduction of PrEP, an extremely efficacious drug, coincide with a plateau in previously-declining HIV infections? We show that racial disparities in both HIV transmission and PrEP use contribute to the drug's low real-world impact. Our counterfactual analysis demonstrates that if non-White MSM had experienced the same HIV trajectory as White MSM, the post-2012 plateau would have been replaced by a continued decline, preventing 44,000 infections among MSM between 2012 and 2022. While Black and White men are equally likely to use PrEP, Black MSM are eight-times more likely to contract HIV, indicating substantial underutilization relative to need.

To understand the consequences of racial disparities in PrEP utilization, we analyze the geographic distribution of White and Black male same-sex partnerships. Overall same-sex partnership share strongly correlates with White same-sex partnership share ($\rho = 0.97$) but is a weaker predictor of Black same-sex partnership share ($\rho = 0.50$). In addition,

counties with higher concentrations of White same-sex partnerships exhibit greater PrEP uptake; those with more Black same-sex partnerships do not. As a result, HIV diagnoses continued to decline among the former, but we detect no reduction in transmission rates in counties with higher concentrations of Black same-sex partnerships. We then analyze data on pharmaceutical payments and from CDC surveillance surveys to rule out two potential causes of PrEP underutilization: differential marketing by the manufacturer and racial gaps in PrEP awareness. Instead, the racial disparity in PrEP uptake mirrors broader disparities in preventive care use, including Mpox vaccinations and primary care visits. These parallels point to factors beyond individual awareness or marketing, such as medical mistrust, as contributors to this racial disparity.

Finally, we show the introduction of PrEP was associated with an increase in risky sexual behaviors among both users and non-users. By reducing the expected cost of sexual risk-taking, PrEP not only induced users to engage in condomless sex but also influenced the behavior of non-users. Motivated by a social-spillovers hypothesis, we analyze condom use data for MSM and heterosexual men and observe a plunge in condom use among MSM following PrEP's introduction; there is no change among heterosexual men. Notably, the magnitude of this decline exceeds the proportion of PrEP users, suggesting that shifts in sexual norms within the MSM population may have led to wide-ranging increases in sexual risk-taking that blunt PrEP's real-world effectiveness.

Our paper makes three novel contributions. First, we provide empirical evidence on the causal impact of PrEP's introduction on HIV incidence, distinguishing between its clinical efficacy and real-world effectiveness. Using a synthetic-control strategy and leveraging geographic variation in male same-sex partnerships, we show that while uptake reduces new diagnoses among MSM, its benefits are not fully reflected in aggregate trends. Medical and epidemiological studies have sought to estimate PrEP's impact on population-level incidence but rely on small samples or single localities, such as one county, limiting their generalizability (Grulich et al., 2018; Johnson et al., 2019; Pagkas-Bather et al., 2021; Koss et al., 2021). Our study utilizes reliable, nationwide surveillance data on HIV diagnoses and PrEP use. Additionally, many of these studies lack appropriate comparison groups and do not account for secular trends in diagnoses, complicating their causal interpretations (Jourdain et al., 2022; Estcourt et al., 2021; Van Epps et al., 2019). We provide a well-identified approach for addressing selection bias in PrEP uptake to quantify the real-world effectiveness of this important medical innovation.

Our paper also advances the literature on the economics of HIV and related infectious diseases. Raman et al. (2022), for instance, show that states expanding Medicaid through

the Affordable Care Act experienced lower transmission partly due to enhanced PrEP access, though this channel is difficult to disentangle from simultaneous improvements in HIV treatment and testing. Similarly, Mann (2023) examines the staggered adoption of PrEP guidelines in Europe, but varying HIV prevalence across countries complicate efforts to draw conclusions about the plateau in incidence observed in the U.S. Researchers have also investigated PrEP's effects on other sexually transmitted infections (Eilam and Delhommer, 2022), the impact of Highly Active Antiretroviral Therapy (Lakdawalla et al., 2006; Chan et al., 2016; Shahid, 2023; Beheshti et al., 2025; Duggan and Evans, 2008), the role of stigma and social norms (De Walque et al., 2014; Yang et al., 2023; Banerjee et al., 2019), and how Ryan White funding helped curb the HIV epidemic (Dillender, 2023). While Ryan White funding for cities meaningfully lowered HIV morbidity and mortality in the U.S., the impact of PrEP's introduction has been far more modest.

Second, this paper contributes to our understanding of the efficacy-effectiveness gap in medical interventions. While PrEP demonstrates near-perfect efficacy in clinical trials, its real-world impact has fallen short of expectations (Bor and Thirumurthy, 2019). Prior work has documented similar declines in effectiveness when interventions are scaled outside controlled settings, including vaccines (Plotkin, 2014; Osterholm et al., 2012; Bauch and Galvani, 2013), behavioral health programs (Depp and Lebowitz, 2007; Dupas and Miguel, 2017), and even microfinance (Banerjee et al., 2015; Morduch, 1999) and educational interventions (Jepsen and Rivkin, 2009; Muralidharan and Singh, 2020; Bold et al., 2018). These gaps have been attributed to a range of factors, including suboptimal policy design (Jobjörnsson et al., 2016; Goehring and Hanlon, 2024), misaligned financial incentives for firms (Oostrom, 2024), underrepresentation (Alsan et al., 2024), and placebo effects (Malani, 2006). While we find significant declines in HIV incidence in areas with higher rates of PrEP adoption, our analysis highlights how heterogeneous uptake and adverse behavioral effects can attenuate the real-world effects of even the most promising interventions.

Finally, our findings connect to a rich body of evidence on the causes and consequences of racial health disparities. We document how uneven PrEP uptake by race stalls progress in combating the HIV epidemic, which disproportionately impacts Black men in the U.S. The determinants of health disparities are complex (Cutler et al., 2006) and include factors such as the health care delivery system (Alsan et al., 2024; Corredor-Waldron et al., 2024; Chandra et al., 2024), medical bias and discrimination (Benitez et al., 2024; Eli et al., 2023; Hoffman et al., 2016), labor market forces (Carey et al., 2023; Grooms et al., 2022), and geography (Chandra and Skinner, 2003; Gillingham and Huang, 2024). We show that Black-White gaps in PrEP uptake are not associated with marketing efforts by pharmaceutical

manufacturers or differences in PrEP awareness. Rather, lower uptake of PrEP among Black MSM may reflect the same forces that affect the utilization of preventive care among Black men more broadly. Our study extends the analysis of health inequities, showing that medical innovations aimed at reducing the burden of diseases affecting Black communities, such as HIV, do not necessarily narrow health disparities. In fact, if adoption is extremely uneven relative to need, then innovations can widen disparities.

The remainder of the paper is organized as follows. Section II provides context on the HIV epidemic and introduces a model to understand transmission dynamics under a PrEP regime. Section III describes our data and presents summary statistics. Section IV outlines our empirical strategy and identifying assumptions. Section V estimates PrEP's real-world effectiveness, while Section VI investigates the causes of disparities in PrEP uptake. Section VII evaluates evidence of behavioral spillovers that attenuate PrEP's effectiveness. Section VIII concludes with policy implications.

2 Background

2.1 The HIV Epidemic in the U.S.

The human immunodeficiency virus (HIV) is a chronic, incurable condition transmitted through unprotected sex, needle sharing, blood transfusions, and from mother to child during pregnancy or breastfeeding. The virus attacks the immune system by targeting white blood cells, and in the absence of treatment, most individuals progress to acquired immunodeficiency syndrome (AIDS) within 8 to 10 years. Individuals with AIDS face a high risk of opportunistic infections and cancers. Once a fatal illness in the early 1980s, advances in antiretroviral therapy have transformed it into a manageable chronic condition (CDC, 2024b). Despite these medical advances, HIV remains a persistent and costly public health challenge. The U.S. spends $35 billion annually on HIV/AIDS programs, with 62% dedicated to domestic care and treatment (Foundation, 2019). Beyond the direct costs averaging $420,285 (in 2019 USD) per HIV infection (Bingham et al., 2021), individuals and families also experience lost productivity, reduced quality of life, and stress (Schackman et al., 2015).

Globally, 40 million people live with HIV, and the virus is responsible for 630,000 deaths annually (WHO, 2022). In the U.S., 1.1 million are infected, including 13% who remain unaware of their status. New diagnoses have declined marginally, from 40,188 in 2012 to 37,601 in 2022, with 18,937 Americans dying from HIV-related causes in 2022 alone, a 19%

increase from a decade earlier. Men who have sex with men (MSM)[2] face a disproportionate disease burden, accounting for 82% of new HIV diagnoses among men in 2022, with a lifetime infection risk of one-in-six — far higher than the one-in-524 risk for heterosexual men (CDC, 2021). Racial and ethnic disparities are also stark: Black and Hispanic MSM face lifetime risks of one-in-two and one-in-four, respectively.[3]

Over the past three decades, public health strategies, ranging from expanded testing and linkage-to-care initiatives to educational campaigns and safe-sex programs, have contributed to reducing HIV infections from their peak in the 1990s (Frieden et al., 2005). Yet, despite these efforts, the rate of decline in new diagnoses has been modest, and the epidemic continues to exert a toll on public health. The introduction of PrEP in 2012 added a new tool to the array of prevention efforts, offering near-complete protection against HIV when used consistently. However, incidence data suggest that even this promising intervention, alongside other strategies, has been insufficient to eliminate new infections or fully contain the epidemic.

2.2 Introduction of PrEP as a Prevention Tool

Pre-exposure prophylaxis (PrEP) refers to the category of antiretroviral drugs taken by HIV-negative individuals to reduce the risk of contracting HIV. Three drugs are currently approved by the U.S. Food and Drug Administration: Truvada (2012), Descovy (2019), and Apretude (2021). Truvada and Descovy are taken orally, and Apretude is administered as a bimonthly injection. Clinical trials estimate that consistent use reduces sexual HIV acquisition by 99% (CDC, 2024c), with protection even under suboptimal adherence (Anderson et al., 2012; Grant et al., 2014). Maximum efficacy is reached seven days after starting daily treatment. PrEP is generally well tolerated, with only mild, transient side effects, and rare renal or bone effects that reverse upon discontinuation (Tetteh et al., 2017; Pilkington et al., 2018). Most private insurers and state Medicaid programs cover the cost of PrEP, including related visits and lab tests.[4] Uninsured adults can obtain PrEP at low or no cost via

[2]MSM is a term used in public health to describe sexual behavior rather than identity, encompassing gay, bisexual, and other men who engage in same-sex sexual activity.

[3]Black and Hispanic individuals represent 40% and 29% of new HIV diagnoses in the U.S., while making up only 12% and 19% of the population, respectively. These disparities are associated with differences in access to HIV prevention and treatment, higher prevalence rates within sexual networks, and barriers to health care. Additionally, HIV-positive Black and Hispanic individuals are more likely to experience delayed diagnosis and treatment.

[4]In 2019, PrEP received an "A" rating from the U.S. Preventive Services Task Force under the Affordable Care Act, meaning most insurers are required to cover PrEP with little to no cost-sharing for the insured patient.

assistance programs, although prior research identified cost as a barrier for some (Kay and Pinto, 2020; Luthra and Gorman, 2018).

Since its regulatory approval in 2012, PrEP adoption has expanded in the U.S. By 2022, approximately 450,000 individuals were actively using PrEP (Sullivan et al., 2020). With increasing treatment options, growing awareness, and declining costs, usage is projected to continue rising. Additionally, the federal initiative Ending the HIV Epidemic: A Plan for America, launched in 2019, aims to reduce new HIV infections by 90% by 2030. A key component of this initiative is expanding PrEP access to 1.2 million high-risk individuals, though as of 2020, only 25% of those were using the drug (Powder, 2022; HIV.gov, 2022; Beyrer et al., 2021).

Because MSM account for most new HIV infections in the U.S., this demographic has been the primary target of efforts to take up PrEP. Of the 1.2 million adults deemed high-risk candidates for the drug, MSM comprise the largest group at 41% (Siegler et al., 2018).[5] A 2023 CDC survey of 4,451 HIV-negative MSM found that 93% were aware of PrEP, and 45% had used it in the past year (CDC, 2024a). In Section 5, we also demonstrate that county-level concentrations of male same-sex partnerships are strongly correlated with higher PrEP uptake. Although PrEP is also recommended for high-risk heterosexual women, men, and people who use injection drugs, uptake in these groups remains low.[6]

2.3 Modeling HIV Transmission

This section outlines a Susceptible-Infected-Removed model for HIV transmission, forming the theoretical basis for our empirical strategy (Nelson and Williams 2014). Let S_t, I_t, and R_t denote the proportions of the population that are susceptible to HIV, currently infected, and removed (i.e., no longer engaging in risky sexual activity and/or receiving treatment that renders them undetectable and non-infectious) at time t, respectively. HIV transmission is governed by two parameters: the infection rate β (the product of the sexual contact rate and per-contact transmission probability) and the removal rate γ. The progression of HIV

[5]Of the 1.2 million, 492,000 are MSM, 468,000 are heterosexual women, 157,000 are heterosexual men, and 115,000 are people who use injection drugs.

[6]For example, only 7.8% (34,428) of PrEP users in 2022 were female (Sullivan et al., 2020), and less than 3% of people who inject drugs use PrEP (Mistler et al., 2021).

over time follows the system of differential equations:

$$\frac{dS_t}{dt} = -\beta S_t I_t, \tag{1}$$

$$\frac{dI_t}{dt} = \beta S_t I_t - \gamma I_t, \tag{2}$$

$$\frac{dR_t}{dt} = \gamma I_t \tag{3}$$

We introduce the fraction p_t of the susceptible population at time t that uses PrEP, reducing their probability of infection by an efficacy parameter $\theta \in [0, 1]$:

$$\frac{dI_t}{dt} = \beta \left[(1-\theta)p_t S_t + (1-p_t)S_t\right] I_t - \gamma I_t = \beta \left[1 - \theta p_t\right] S_t I_t - \gamma I_t \tag{4}$$

This modification captures how PrEP alters HIV transmission dynamics by effectively lowering the infection rate among protected individuals. The closed-form solution for I_t becomes:

$$I_t = I_0 \exp\left(\int_0^t \left(\beta \left[1 - \theta p_s\right] S_s - \gamma\right) ds\right) \tag{5}$$

Although clinical trials provide an estimate of PrEP's efficacy θ in preventing HIV transmission, according to our model, its real-world effectiveness may diverge due to several factors. First, because HIV is an infectious disease, an individual's decision to adopt PrEP has externalities. Those who use PrEP, $p_t S_t$, reduce their likelihood of contracting HIV, which in turn lowers transmission risk for others in the population, including those who do not use the drug, $(1-p_t)S_t$. This channel would increase real-world effectiveness. Second, behavioral responses among the protected population, such as increased sexual risk-taking due to moral hazard, may lead to higher contact rates or reduced condom use, endogenously increasing β. Changes in risk-taking norms may also spill over into the unprotected population. Finally, PrEP adoption may be unevenly distributed across risk groups; higher-risk populations may underutilize PrEP while lower-risk groups adopt it more readily.[7] Both of these channels would lower real-world effectiveness. In Appendix A.1, we develop a multi-type model to account for differential risk and PrEP adoption between groups.

Using this framework, we demonstrate that PrEP's real-world effectiveness depends not

[7]For instance, the same factors that lower an individual's risk of HIV contraction, such as higher education, greater access to health care, and a more risk-averse lifestyle, may also make them more likely to adopt PrEP. However, assuming θ is constant across individuals, effectiveness is maximized when the highest-risk individuals use PrEP. This selection pattern aligns with a general reverse-Roy model, in which individuals self-select into interventions based on underlying risk profiles that inversely correlate with anticipated benefits. (Heckman and Honore, 1990; Cornelissen et al., 2018).

only on its clinical efficacy θ but also on the distribution of p_t and any endogenous shifts in β induced by PrEP's introduction. For example, risk compensation can cause effectiveness to fall short of clinical predictions. In equilibrium, HIV incidence is sensitive to which subpopulations adopt PrEP; inadequate access among high-risk groups, relative to their baseline risk, may also limit overall reductions in HIV rates. These theoretical insights guide our empirical analysis.

3 Data and Descriptive Statistics

3.1 Data Sources

HIV diagnoses. We obtain HIV diagnosis data at the county (year × sex × race) and national (year × sex × race × transmission) levels from the CDC AtlasPlus database.[8] HIV diagnoses refer to the number of individuals newly diagnosed with HIV in a given year, no matter the year of infection. We compute HIV diagnosis rates per 10,000 individuals. For men, transmission categories include male-to-male sexual contact, heterosexual contact, injection drug use, male-to-male sexual contact plus injection drug use, and "other". To be included in our primary analysis, a county must have no missing or suppressed observations in each year from 2008 through 2022, yielding a sample of 321 counties. Although this set represents only about 10% of all U.S. counties, they account for 76 to 79% of nationwide HIV diagnoses, since more populous counties are less likely to have suppressed data.[9] We use the full 2008–2022 sample, though some analyses exclude data from 2020 due to disruptions in HIV testing and surveillance during the COVID-19 pandemic.

PrEP uptake. We obtain data on PrEP users at the county (year × sex) and the national (year × sex × race) levels from AIDSVu (Sullivan et al., 2020).[10] These datasets were compiled from a national sample of patient-level prescription data.[11] We compute PrEP usage rates per 10,000 individuals. An individual is classified as a "PrEP user" in a given

[8]The CDC AtlasPlus is a query platform providing nationwide, state, and county-level statistics on HIV, viral hepatitis, STIs, and tuberculosis. Updated annually, its data examines demographic and geographic trends in these conditions over time.

[9]Data suppression is more common in counties with very low case counts.

[10]AIDSVu is partnership between Emory University's Rollins School of Public Health and Gilead Sciences, the producer of PrEP. The number of PrEP users by race is unavailable at the county-year level, due to small sample sizes and privacy concerns.

[11]The sample includes more than 54,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices across the U.S. It encompasses all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid.

year if he or she receives a 30-day prescription that overlaps with that year. Following the methodology from Sullivan et al. (2020), we also calculate the PrEP-to-need ratio by dividing the number of PrEP users in year t by HIV diagnoses in year $t-1$, allowing us to measure PrEP coverage relative to local HIV transmission risk. A lower PrEP-to-need ratio indicates comparatively inadequate coverage.

Male same-sex partnerships. We proxy the share of MSM in a county by calculating the proportion of male same-sex partnerships among all partnerships, using data from the American Community Survey and Decennial Census for 2000–2015 (excluding 2001–2004 due to comparability issues).[12] To do this, we identify households with two partnered or married adults and classify those where both adults are male as male same-sex partnerships. For each county, we compute shares by dividing the number of these partnerships by the total number of partnerships. Although this statistic only captures men in same-sex relationships, a group that may be less likely to use PrEP, counties with higher shares tend to be more socially inclusive and feature queer-friendly amenities, attracting younger, sexually active MSM (Rosenberg et al., 2016).

Our male same-sex partnership measure is available for 475 counties, which account for roughly 68% of all male same-sex partnerships nationally. We also calculate these shares by race. To validate our proxy, we compare it with Gallup's state-level estimates of the population identifying as gay, lesbian, bisexual, or transgender (Gates and Newport, 2013) and find a very strong correlation ($\rho = 0.82$), indicating that our measure reliably ranks counties by the size of their MSM population. Figure 4 displays counties ordered by their share of male same-sex partnerships, which ranges from 0.18 to 5.02. The top four — San Francisco, District of Columbia, New York, and Suffolk — are known for their large MSM populations.

3.2 Summary Statistics

Table 1 displays summary statistics for the N counties included in our analysis. We divide counties into quartiles based on their share of male same-sex partnerships and report the mean values of key variables for each quartile. Estimates are provided separately for the periods before and after PrEP's introduction in 2012 (panels (a) and (b), respectively). Several striking differences emerge. First, counties with a higher share of male same-sex partnerships experience substantially higher HIV diagnosis rates, a finding that aligns with

[12]Specifically, we use the 2000 5% Census sample, 2009 5-year ACS (2005–2009), 2010 10% Census sample, and 2015 5-year ACS (2011–2015); see Ruggles et al. (2024) and Bureau (2009).

the concentration of HIV transmission among MSM. Second, following the introduction of PrEP, these counties show higher rates of PrEP use. As we describe in the following section, this variation in male same-sex partnership shares is central to our empirical strategy. Third, demographic characteristics differ notably: counties with higher shares tend to have larger populations, a greater proportion of Black residents, and a smaller proportion of White residents.

The table also highlights dynamics in HIV diagnosis rates over time. Among the lowest quartile of male same-sex partnership share, there is little change between the pre- and post-PrEP periods. In contrast, each higher quartile shows a progressively larger decline in HIV diagnoses over time. This pattern, together with increased PrEP uptake, suggests a causal role of PrEP in reducing HIV incidence. We test this hypothesis in Section 5.

3.3 Descriptive Evidence on the Evolution of PrEP and HIV

We begin by presenting a series of descriptive figures highlighting the puzzle surrounding HIV incidence following PrEP's regulatory approval. In Figure 1, blue markers plot the number of PrEP users per 10,000. Although adoption was initially slow, PrEP use in the U.S. grew considerably over time. Still, the absolute number of users remains modest, reflecting the fact that PrEP is primarily targeted at sexually active MSM, a very small fraction of the overall population. By 2022, the CDC estimated that only about 36% of those recommended for PrEP were actually using it (CDC 2024). The same figure plots the annual rate of new HIV diagnoses per 10,000 in black. Prior to PrEP's introduction, HIV diagnoses were steadily declining. Given PrEP's near-perfect clinical efficacy, many expected this downward trend to accelerate once the drug became available. To illustrate this, we extrapolate the pre-2012 trend into the post-PrEP period. Instead of a faster decline, however, the HIV diagnosis rate plateaued beginning in 2013. This flattening of the trend, despite the increasing uptake of an efficacious prevention drug, presents a puzzle that motivates our subsequent empirical analysis.

Panel A of Figure 2 dissects PrEP usage by sex. Blue represents the rate of female users per 10,000, and black represents the rate of male users. As discussed in Section 2, nearly all PrEP users are MSM. By the end of 2022, the number of men using PrEP was 12 times the number of women using the drug. Panel B introduces the PrEP-to-Need ratio, a metric that adjusts for risk by comparing the number of PrEP users to the number of HIV diagnoses from the previous year. While the male-female disparity in the PrEP-to-Need ratio is not as pronounced as in the raw number of users, the male ratio remains nearly three times the

female ratio by the final year of our sample. This likely reflects the fact that PrEP marketing and outreach have focused on MSM.

Given the nonuniform demographics of PrEP usage, could differences by sex or sexual orientation be obscuring the drug's impact in these aggregate statistics? Panel (a) of Figure 3 explores this possibility. Because HIV diagnosis rates are significantly higher among men than women, we normalize the 2011 rates to 100% for both groups and then trace their subsequent evolution: gray for women and blue for men. Both groups exhibit a clear pre-2012 decline, with the decline being steeper for women. Yet, after PrEP became available, no evidence suggests any further reduction in diagnoses among men, either relative to their previous trend or in comparison to women.

Panel (b) disaggregates male HIV diagnoses by transmission category. Since PrEP is primarily targeted at MSM, any beneficial effect should be most apparent in this subgroup. After normalizing the 2011 rates, we plot diagnoses caused by male-to-male sexual contact in blue and those from heterosexual contact in red. While heterosexual men continued to experience a decline in HIV diagnoses throughout the pre-2012 period, the rate for MSM remained largely flat before 2012 and showed almost no change thereafter. Prima facie, Figures 1 through 3 appear inconsistent with the argument that PrEP's introduction led to a significant reduction in HIV transmission rates. Although aggregate HIV incidence was declining before PrEP's introduction and then stalled afterward, the expected post-PrEP drop, especially among men and specifically among MSM, is absent. In the next section, we outline our empirical approach to disentangle these relationships and rigorously estimate the real-world effectiveness of PrEP.

4 Empirical Strategy

This section outlines our empirical strategy for estimating the real-world effectiveness of PrEP. Our goal is not to measure the drug's clinical efficacy, which has been established in numerous clinical trials (Table A3.1), but rather to assess how its regulatory approval in 2012 influenced HIV outcomes at the population level. The key challenge in identifying this causal effect arises from the fact that PrEP utilization is concentrated among individuals at higher baseline risk for HIV. A naïve regression of HIV transmission on PrEP adoption would likely suffer from upward bias, suggesting that PrEP increases HIV incidence.

4.1 Event Study Model

To address this selection bias, we exploit two key empirical facts. First, PrEP is almost exclusively marketed toward and adopted by MSM. Second, the prevalence of male same-sex partnerships varies substantially across regions of the U.S. This geographic heterogeneity, combined with the timing of PrEP's approval in 2012, allows us to compare shifts in HIV transmission across counties differentially exposed to the drug over time. Figure 4 illustrates this variation by ranking counties according to their share of male same-sex partnerships. While the median county has a same-sex partnership share of 0.47%, San Francisco County and the District of Columbia exceed 4%.

Counties with higher pre-existing concentrations of male same-sex partnerships were more exposed to PrEP's introduction than counties with lower concentrations. Our identification strategy compares trends in HIV transmission across counties that, ex ante, were more likely to adopt PrEP versus those that were not, before and after 2012. We hypothesize that counties with higher concentrations of male same-sex partnerships experienced greater uptake of PrEP, and that this differential exposure are reflected in subsequent HIV outcomes. Consider the following event-study specification:

$$y_{ct} = \alpha_c + \gamma_t + \sum_{\tau \neq 2011} \beta_\tau \cdot 1(t = \tau) \cdot MSSP_c + \epsilon_{ct} \tag{6}$$

where y_{ct} is an HIV-related outcome for county c in year t. County and year fixed effects are α_c and γ_t, respectively. $MSSP_c$ is the concentration of male same-sex partnerships in each county, as defined in section 3. The vector β_T are coefficients on a set of interaction terms between year fixed effects and $MSSP_c$, with 2011 normalized to zero. The coefficients capture the gap in y_{ct} between counties with larger versus smaller $MSSP_c$ concentrations in each year, relative to 2011. This specification allows for dynamic treatment effects, recognizing that PrEP use increased gradually and that its impact on HIV transmission might take time to materialize given the nature of infectious diseases (refer to Section 2.3).

A standard difference-in-differences approach for estimating β_τ would assume that, in the absence of PrEP's introduction, HIV rates in all counties with high versus low concentrations of male same-sex partnerships would have evolved in parallel. Yet, given well-documented differences in HIV epidemiology across sex and sexual orientation (Valleroy et al., 2000), this parallel trends assumption is ill-suited for our setting. Violations of this parallel-trends assumption would lead to biased estimates of β_τ.

To address this concern, we implement a synthetic-control estimator, following Powell (2022). We proceed in four steps:

1. For each county c, construct a synthetic county $\tilde{c}$ as the convex combination of donor counties, using weights that minimize the root mean square error in HIV rates between c and $\widetilde{c}$ between 2008 and 2011. The reliability of the synthetic-control approach depends on closely matching pre-2012, we drop the 5% of counties with the worst pre-period matches based on the root mean squared error, following (Abadie et al., 2010).

2. Construct synthetic variables $\widetilde{y_{ct}}$ and $\widetilde{MSSP_{ct}}$ using the weights generated in step 1.

3. Define $\dot{y_{ct}} \equiv y_{ct} - \widetilde{y_{ct}}$ and $\dot{MSSP_c} \equiv MSSP_c - \widetilde{MSSP_c}$. By differencing out the synthetic outcome and synthetic treatment variable, we remove differential pre-treatment trends in HIV rates across counties, and estimate the treatment effect net of these trends.

4. Estimate the event-study equation (6) using the residualized variables computed in step 3 using ordinary least squares.

To account for the multi-step nature of our estimation procedure, we construct confidence intervals for our synthetic-control estimates using the bootstrap approach proposed by Abadie et al. (2010). Specifically, we draw 200 bootstrap resamples from the original dataset with replacement, repeating the synthetic-control procedure for each resample. For each resample, we identify the optimal donor pool by calculating the weights that minimize pre-period root mean squared error, construct synthetic counterparts, and estimate the event-study equation. Finally, we construct 95 percent confidence intervals by taking the 2.5 and 97.5 percentiles of the empirical distribution of our bootstrapped estimates (Ferman and Pinto, 2021; Powell, 2022).

For exposition, consider the construction of a synthetic counterpart for San Francisco County, which has the nation's highest concentration of male same-sex partnerships. Synthetic San Francisco is composed of 23% Orleans Parish (LA), 17% the District of Columbia (DC), 12% Lowndes County (GA), with the remaining 49% drawn from other donor counties. These weights were chosen to ensure that pre-2012 HIV rates in the synthetic county closely match those observed in San Francisco. While San Francisco's actual male same-sex partnership share is 5.0%, its synthetic counterpart only has a 1.6% share. This divergence, despite matching pre-2012 HIV trends, is key for identifying β_τ in our event-study specification. In effect, the synthetic control isolates the impact of PrEP by comparing San Francisco's demographic composition to a counterfactual constructed to have the same HIV trajectory before PrEP's introduction.

Why does San Francisco exhibit a markedly higher concentration of male same-sex partnerships compared to its synthetic counterpart? History offers an explanation. San Francisco's early prominence as a port city and military hub during World War II, followed by its role as a processing center for personnel discharged from the armed forces, many of whom for their sexual orientation, helped establish a large gay community in the region. Over time, the presence of this community, a growing network of queer-friendly amenities, social spaces, and political activism further attracted MSM, reinforcing a cycle that continues to shape the city's demographics today. This example demonstrates how differences in demographics, even when HIV transmission trends are matched, can be leveraged using a synthetic-control method to identify the impact of PrEP's introduction.

4.2 Identifying Assumption

Our synthetic-control strategy requires that, in the absence of PrEP's introduction, a county's HIV trajectory would have evolved in parallel with that of its synthetic counterpart. Formally, this implies that $\dot{y}_{ct} = 0$ without PrEP. Our approach constructs each synthetic control by assigning weights to a set of donor counties so that the pre-2012 HIV trend matches that of the target county. By design, the estimator minimizes the mean squared error between pairs of real and synthetic counties, controlling for pre-2012 and time-invariant factors, such as existing health infrastructure and other determinants of county-level variation in HIV transmission, reducing the influence of such confounders on any post-2012 differences.

If, for example, a county's HIV trend were driven solely by long-standing historical factors, then its outcomes after 2012 would continue to mirror those of its synthetic counterpart. However, we observe divergences following PrEP's introduction, which we interpret as being driven by differential uptake of PrEP due to varying concentrations of male same-sex partnerships. Importantly, the factors shaping these demographic patterns, such as historical migration trends and legacies from military discharge practices dating back decades, were well established long before PrEP became available.

We validate this identifying assumption in two ways. First, we perform placebo tests on groups with minimal PrEP uptake: women and heterosexual men. If unobserved, post-2012 county-level shocks were driving for our findings, then we would expect to observe similar treatment effects in these groups. Instead, as Figure 7 shows, the estimated treatment effects for women and heterosexual men are statistically indistinguishable from zero (see Section 5.1 for an expanded discussion). By 2022, the coefficients for women and heterosexual men are -0.06 and -0.09, roughly one thirteenth and one tenth of the coefficients for all men and

MSM, respectively.[13] That we find significant effects only among groups that use have high PrEP uptake, and that the magnitudes of the declines in HIV rise with the magnitudes of PrEP uptake suggests that our results are in fact a causal result of PrEP.

Second, we examine counties whose synthetic control, due to chance inherent in the weighting procedure, closely matches the target's male same-sex partnership concentration. The idea here is to compare counties with similar male same-sex partnership concentrations, which should be similarly affected by PrEP's introduction. As detailed in Appendix A.2, counties with matches in the middle two deciles of the distribution of actual minus synthetic male same-sex partnership concentration show no significant changes in PrEP uptake (mean difference = 0.24, 95 % CI = [-1.17, 2.16]) or PNR (mean difference = -1.18, 95 % CI = [-3.56, 2.26]). Given the lack of differential PrEP uptake or PNR in these counties, we would not expect any difference in HIV diagnosis rates, which is precisely what we find (mean difference = -0.02, 95 % CI = [-0.15, 0.16]). In contrast, counties with poorer matches (i.e., meaningful differences in actual and synthetic male same-sex partnership concentrations) exhibit significant divergences in PrEP uptake and PNR. These divergences correspond with divergences in HIV that are in the expected directions. These findings indicate that our synthetic-control results are indeed identified on differential PrEP uptake driven by variations in male same-sex partnership concentrations. Together, these exercises support our identifying assumption that, in the absence of PrEP's introduction, a county's HIV trajectory would have evolved in parallel with that of its synthetic counterpart.

5 Results

5.1 PrEP's Real-World Effectiveness

First stage. We begin by showing that counties with higher concentrations of male same-sex partnerships experience higher PrEP uptake than counties with lower concentrations. To do this, we estimate equation (6) for the rate of PrEP users.[14] Panel A of Figure 5 presents coefficients that are mechanically zero before 2012; after PrEP's introduction, the coefficients reveal rapid growth in uptake that persists through 2022. Year fixed effects absorb trends common to all counties, so these positive and meaningful coefficients reflect differential

[13] In reality, the heterosexual estimate is likely dramatically smaller than the MSM coefficient, as we use all men in the denominator when computing the HIV diagnosis rate among MSM.

[14] Because PrEP usage is zero for all counties before 2012, any convex combination of counties yields a perfect synthetic control. In these figures, we use weights determined by matching on pre-2012 HIV diagnosis trends, as discussed in Section 4.

increases in PrEP uptake in areas with larger shares of male same-sex partnerships. Our coefficient estimate of 24 in 2022 implies that for each percentage-point increase in the share of male same-sex partnerships, there are, on average, 24 additional PrEP users per 10,000 that year.

In Panel B, we replicate this analysis by sex. Virtually all the cross-county variation in PrEP uptake occurs among men. In 2022, the estimated coefficient for men is 47.02, compared to only 1.05 for women. This result is consistent with descriptive evidence that PrEP is targeted toward and almost exclusively used by MSM, who bear a disproportionately high disease burden. Moreover, this result serves as a compelling placebo test for our identifying assumption; since women are roughly 50 times less likely to use PrEP, our empirical strategy should not detect shifts in new HIV diagnoses for this group.

We also analyze the risk-adjusted PrEP-to-need ratio, defined as the number of PrEP users divided by new HIV diagnoses in the previous year. Panels C and D present these results for the full sample and separately by sex, respectively. In 2022, the coefficient for men is 13.8 compared to 5.3 for women. That is, even after adjusting for risk of HIV transmission, men in areas with higher concentrations of male same-sex partnerships are significantly more likely to use PrEP. The findings from this section make two important points: first, PrEP uptake has been concentrated in counties with disproportionately high shares of MSM, and second, PrEP uptake is almost exclusively driven by men. We now turn to our estimates of how PrEP's rollout affected HIV transmission.

HIV diagnoses. Our main result is presented in Figure 6, where the outcome is the rate of new HIV diagnoses per 10,000. Prior to PrEP's introduction in 2012, the coefficients are small and statistically insignificant, confirming that our synthetic-control procedure successfully constructed counterfactuals that replicate the pre-PrEP HIV dynamics across counties. This match gives us confidence that subsequent divergences in outcomes are likely due to the drug's introduction rather than to time-invariant or pre-existing differences across counties. In the first two years after PrEP's approval, when uptake remained low, the coefficients are indistinguishable from zero. Beginning in 2014, the coefficients begin to grow in magnitude and become statistically distinguishable from zero for every year after 2016. In 2022, the coefficient is -0.31, implying that a one percentage-point increase in the share of male same-sex partnerships, a proxy for greater PrEP exposure, is associated with 0.31 fewer HIV diagnoses per 10,000. To contextualize this, we form a Wald-style estimator by dividing the 2022 coefficient by the corresponding coefficient from Panel A of Figure 5. The Wald estimate is -0.013, suggesting that 76 additional PrEP users avert one new HIV diagnosis.

Analyzing HIV diagnosis rates has two limitations. First, the outcome does not perfectly capture true disease incidence, as many HIV-positive individuals remain undetected. In 2022, an estimated 13% of people living with HIV in the U.S. were undiagnosed. Second, PrEP may alter HIV testing behavior. For example, if increased testing accompanies PrEP adoption, then more cases could be diagnosed even in the absence of a true change in incidence. We discuss these limitations and their potential impact on our results in Appendix A.3.

In addition, we perform two sensitivity exercises. First, we re-run our analyses substituting CDC estimates of HIV incidence for diagnosis rates.[15] Both measures are nearly perfectly correlated ($\rho = 0.97$), and our results remain unchanged for the subset of counties with incidence data (Appendix Figures A3.10 and A3.11). Second, we examine HIV testing data from the Behavioral Risk Factor Surveillance System spanning 2008 to 2022, and find no differential change in HIV testing rates between men and women following PrEP's introduction (Figure A3.13). This result is somewhat surprising as PrEP prescriptions often require testing for sexually transmitted infections, but it likely reflects the high baseline testing rates among PrEP candidates prior to 2012. Finally, if PrEP did indeed lead to additional HIV testing, this would attenuate our main results because counties with higher PrEP uptake would register more diagnoses relative to their actual incidence.

HIV diagnoses by sex. Both the overall PrEP use rate and the PrEP-to-need ratio are substantially higher for men than for women (Panels B and D of Figure 5). If PrEP's introduction causally lowered HIV transmission, then we expect this effect to be most pronounced among men. In Panel A of Figure 7, which plots event-study coefficients separately for men (blue) and women (gray), we observe a decline in HIV diagnosis rates for men that intensifies over time as PrEP uptake increases. By 2022, the male point estimate is -0.76, indicating that a one standard deviation increase in exposure to treatment is associated with a 0.76 per 10,000 decline in the male HIV diagnosis rate. No such reduction exists among women, a group that rarely uses PrEP, serving as a placebo test for our study design. The female coefficient in 2022 is a statistically insignificant -0.06, roughly one thirteenth the magnitude of the male coefficient. This evidence reinforces the validity of our identification strategy by ruling out the possibility that unobserved, post-2012 county-level shocks affecting men and women are driving our main results.

[15]The CDC AtlasPlus provides estimates of county-level incidence for a subset of 48 counties in our sample. The CDC calculates HIV incidence by using CD4 count data from newly diagnosed individuals to back-calculate the likely year of infection, thereby reconstructing annual incidence trends. This method is limited to counties that have complete and reliable CD4 laboratory reporting, ensuring that the estimates are based on robust data.

HIV diagnoses by sexual orientation. The overwhelming majority of new HIV diagnoses among men occur within the MSM community, even though this group represents only around 5% of the overall male population. In Panel B of Figure 7, we disaggregate male HIV diagnoses into cases for heterosexual men and for MSM. We document little to no change in diagnoses among heterosexual men, likely because they have substantially lower baseline rates and minimal PrEP uptake. Virtually all of the decline in new diagnoses is driven by reductions among MSM. We note that the male coefficients from Panel A are nearly identical to the MSM coefficients in Panel B.

Our real-world findings align with evidence regarding PrEP's clinical efficacy. However, they also raise a puzzlingly question: if PrEP is effective at reducing transmission among MSM, why has its adoption not led to declines in aggregate HIV transmission? Instead, the period after PrEP's introduction coincided with a halt in the previously-consistent fall in transmission rates. We now turn our attention to reconciling the evidence of PrEP's real-world effectiveness with the observed plateau in HIV infections.

5.2 Why Did Aggregate Diagnoses Stop Declining?

Despite evidence that PrEP reduces HIV transmission in counties with large MSM populations, new HIV infections did not fall as steeply as expected after its approval. To understand the disconnect between PrEP's effectiveness and the plateau in diagnoses, we examine the links among infection rates, PrEP uptake, and racial disparities. Three observations motivate our analysis. First, HIV incidence and trends vary significantly by race. Second, while raw measures of PrEP uptake are similar levels across racial groups, risk-adjusted metrics differ. Third, our spatial measure of male same-sex partnerships reflects primarily the experiences of White MSM.

First, Figure 8 illustrates that both the levels and trends in HIV diagnoses among MSM differ by race. Black MSM bear a disproportionate burden of these diagnoses: Black men experience rates 6 times higher than those of White men. Moreover, while HIV cases among White MSM have steadily declined over time, the decline among Black MSM was less pronounced before 2012 and stalled thereafter, stabilizing at 9,000 new cases per year. To demonstrate the importance of these racial disparities, we perform a back-of-the-envelope counterfactual exercise. For each year after 2012, we impose on non-White MSM the same percentage decline in diagnoses observed among White MSM. Appendix Figure A3.6 presents these counterfactual trends. If non-White MSM had experienced the same proportional reductions in HIV diagnoses as White MSM, overall HIV incidence among MSM would have

been cut by nearly one third by 2022.

Second, although raw PrEP uptake rates are similar across racial groups, the PrEP-to-need ratio uncovers a different pattern. Figure 9 shows that when we adjust for the previous year's HIV diagnoses, Black MSM lag behind White MSM in their use of PrEP. By 2022, the ratio for White MSM was roughly 6 times higher than that for Black MSM, highlighting significant underutilization of PrEP among those at highest risk.

Third, the racial composition of counties varies widely. While the national average for the Black population is around 12%, county-level shares range from 0% to 85%. Consequently, our treatment variable — defined by the overall share of male same-sex partnerships — tends to reflect the experiences of White MSM. This is evident in Figure 10: Panel (a) shows a near-perfect correlation ($\rho = 0.97$) between our treatment measure and the fraction of White MSM partnerships, whereas Panel (b) reveals a much weaker correlation ($\rho = 0.50$) for Black MSM. Our baseline measure does not fully capture the higher-risk, underserved Black MSM population.

Motivated by these observations, we now present our main heterogeneity results. We re-estimate our primary synthetic-control regressions using race-specific outcome variables. We also develop models that employ measures of race-specific male same-sex partnerships as our treatment variable. This approach allows us to compare the responses of areas with high shares of White MSM to those with high shares of Black MSM.

5.3 Black-White Disparities in PrEP Uptake

County-by-race data on PrEP uptake are unavailable, but national-level evidence shows that PrEP has been adopted primarily by White men, while Black men have lagged behind. We next examine how PrEP uptake correlates with local levels of race-specific male same-sex partnerships. In particular, we estimate PrEP usage rates in counties with relatively high versus low fractions of White male same-sex partnerships, and then contrast these estimates to those derived using the fraction of Black male same-sex partnerships.

Figure 11 presents our findings. In Panel A, we report the results of our synthetic-control regressions using a standardized measure of White male same-sex partnerships as the treatment variable, and Panel B shows the corresponding results for Black male same-sex partnerships. Each variable is rescaled to have mean zero and standard deviation one. In each panel, the outcome variable is the PrEP usage rate. The results in Panel A are nearly identical to primary results in Figure 5, given the high correlation between our primary treatment measure and the White-specific measure. In contrast, Panel B shows no response

in PrEP uptake associated with higher levels of Black male same-sex partnerships.

The correlation between the White and Black male same-sex partnership variables is 0.43, indicating that counties with large shares of Black MSM also have a substantial presence of White MSM. The near-zero coefficients in Panel B thus suggest that White MSM residing in predominantly Black areas may not be exhibiting higher rates of PrEP uptake. This pattern points to geographic factors as potential drivers of PrEP non-adoption. Panels C and D support this conclusion; analogous analyses using the PrEP-to-need ratio similarly indicate low risk-adjusted PrEP usage in counties with high proportions of Black male same-sex partnerships.

5.4 Black-White Disparities in HIV Diagnoses

We now turn our attention to HIV diagnoses in counties with predominantly White versus predominantly Black male same-sex partnerships. Figure 12 presents results from four separate regressions. First, Panel A reports race-specific HIV diagnosis rates using our White-specific treatment variable. Blue corresponds to White MSM, and gray corresponds to Black MSM. As with our race-specific PrEP results, the estimates for White MSM closely mirror the primary results (Figure 6), consistent with the finding that PrEP has mainly been adopted by White men. The coefficients for Black MSM in these predominantly White areas follow a similar pattern, although they are less precise since fewer of these counties report Black-specific outcome data. One interpretation is that declines in HIV prevalence among White MSM generate spillover benefits that reduce risk for Black MSM, or that Black MSM in predominantly white counties adopt PrEP at higher rates than in other counties. Panel B presents estimates based on Black male same-sex partnerships, where estimates are precisely zero, indicating no reduction in HIV diagnoses in areas with predominantly Black MSM. These results are consistent with the observation that PrEP underutilization has occurred mainly in predominantly Black regions.

These findings indicate that PrEP reduces HIV diagnoses among the populations who use it. However, since counties with high uptake are disproportionately composed of White MSM, who themselves face lower relative risk of contracting HIV, the aggregate impact is muted. In contrast, counties with a higher share of Black MSM, whose infections drive overall HIV trends in the U.S., exhibit low PrEP usage relative to their risk.

6 Mechanisms for Unequal PrEP Uptake

In this section, we discuss three potential mechanisms for why the introduction of PrEP resulted in disparate utilization relative to HIV risk across race and sexual orientation: (i) differential marketing strategies by the manufacturer of PrEP, (ii) gaps in awareness about PrEP, and (iii) disparities in utilization of general preventative care.

6.1 Marketing by the Manufacturer

Like most pharmaceutical firms, Gilead Science — the manufacturer of PrEP — uses a range of marketing strategies to engage health care providers who treat patients indicated for PrEP. One such strategy involves food-and-beverage payments, colloquially known as "drug rep dinners", which serve to introduce the drug to prescribers, updates them on its safety and efficacy, and build relationships that can lead to increased prescriptions. While each payment is modest in value, they amount to $240 million in annual spending (Steinbrook, 2017). Previous studies suggest that these interactions can influence prescribing behaviors (Carey et al., 2021). One hypothesis for PrEP underutilization by Black MSM is that Gilead Science may be under-marketing PrEP in these regions relative to their HIV risk.

To test this hypothesis, we analyze data from the Open Payments database, which is maintained by the Centers for Medicare & Medicaid Services and tracks financial interactions between health care providers and pharmaceutical or medical device manufacturers (CMS 2022). We query all payments disclosed by Gilead Sciences between 2015 and 2019 that were associated with "Truvada" or "Descovy" ($N = 8,418$), with each payment averaging $71. Payments are aggregated at the county level, and we construct a metric of payment-per-diagnosis, which scales Gilead Sciences' marketing intensity in county c by the HIV risk in that county. If Gilead's marketing were uniformly distributed, this metric would be similar across regions regardless of their HIV incidence. We find that payment-per-HIV diagnosis does not vary with the racial composition of counties ($\beta = -0.000169$; $p = XX$). This result suggests that, when accounting for HIV burden, Gilead Sciences' marketing efforts are not disproportionately concentrated in areas with lower shares of Black residents.

6.2 PrEP Awareness

Another hypothesis is that a Black-White gap in PrEP awareness hinders PrEP uptake in high-risk populations. We evaluate this hypothesis using statistics from the 2017 and 2023 waves of the National HIV Behavioral Surveillance system, which monitors HIV-related

behaviors through venue- and respondent-based sampling in high-prevalence urban areas (Cha et al. 2019; Kanny et al. 2023. Between 2017 and 2023, PrEP awareness among Black MSM increased from 78% to 90%, while awareness among White MSM rose from 91% to 96%. However, the narrowing of the racial awareness gap coincided with a widening gap in PrEP utilization between Black and White MSM.

By 2023, awareness of PrEP among MSM approached near-universal levels across both racial groups, with the racial gap in PrEP awareness narrowing to 7 pp. Despite this near-universal awareness, however, the uptake of PrEP among Black MSM did not increase proportionately, resulting in a widening gap in utilization relative to White MSM. These findings challenge the hypothesis that lower awareness is the primary factor driving the underutilization of PrEP among Black MSM relative to their HIV risk.

6.3 Disparities in Preventive Care

Racial disparities in health and preventive care utilization are pervasive among U.S. men (Nelson, 2002; Bailey et al., 2017). For exampple, Black men are less likely than White men to receive influenza immunizations and other preventable vaccinations, contributing to elevated morbidity and mortality (Lu et al. 2015). In addition, Black men experience lower rates of cholesterol screening, hypertension control, and treatment for cardiac conditions (Egan et al., 2014; Vaccarino et al., 2005). These disparities also extend into the MSM population. For instance, during the 2022 Mpox outbreak, Black MSM had significantly lower vaccination rates than their White counterparts (Kota, 2023). Research on STI testing and primary care use indicates that Black MSM receive fewer health services than White MSM (Millett et al., 2012; Levy et al., 2014). The magnitude of these differences mirrors the broader gaps in preventive care utilization between Black and White men, suggesting that the lower uptake of PrEP among Black MSM may reflect the same forces that limit access to preventive care in Black communities.

Multiple factors contribute to these Black-White disparities. Higher rates of poverty and limited health coverage, for instance, restrict access to preventive services (Buchmueller and Levy, 2020; DeVoe et al., 2007). Moreover, historical and ongoing experiences of discrimination, exemplified by events like the Tuskegee Syphilis Study, have deepened mistrust of medical institutions (Alsan and Wanamaker, 2018). Among Black MSM, specifically, social stigma and barriers related to both race and sexual orientation create additional barriers to accessing preventive care, like PrEP (Quinn et al., 2019; Eaton et al., 2015).

7 Risk Compensation and Behavioral Spillovers

PrEP's introduction lowered the cost of engaging in risky sexual behaviors. Because PrEP protects only against HIV, its rollout has been associated with increases in other sexually transmitted infections among men, such as chlamydia, gonorrhea, and syphilis (Eilam and Delhommer, 2022). Similar patterns emerged following the introduction of Highly Active Antiretroviral Therapy to treat HIV (Lakdawalla et al., 2006; Beheshti et al., 2025). These findings align with a model of risk compensation, in which the perceived protection provided by PrEP leads individuals to forgo other protective measures, such as condom use (Cohen and Einav, 2003).

Two mechanisms explain how increased risky sexual behavior among PrEP users could lead to greater HIV incidence in this population. First, many PrEP users do not maintain optimal adherence, a trend that has worsened over time (Tanner, 2020; Unigwe et al., 2024). For example, there is an 80% reduction in infection risk when adherence exceeds 80%, compared with only a 45% reduction at lower adherence levels (Murchu et al., 2022). Second, even with perfect adherence, PrEP does not offer complete protection against HIV transmission.

These behavioral shifts may not be confined solely to PrEP users. By lowering the marginal cost of risky sexual behavior, PrEP may encourage greater risk-taking, reshaping social norms within the MSM population (Bénabou and Tirole, 2011). For instance, a preference for condomless sex may diffuse through sexual networks, normalizing less-safe practices even among non-PrEP users. This behavior can also spread through media consumption, as evidenced by a significant decline in condom use in same-sex pornography following PrEP's introduction (Whitfield et al., 2018). Thus, while PrEP confers direct benefits to users, its network effects may lead to elevated risky behavior that adversely impacts public health.

To examine this hypothesis, we analyze data from the National Health and Nutrition Examination Survey, focusing on condom use among MSM compared to heterosexual men. These data, collected in biennial waves, include self-reported measures of condom use during any sexual encounter in the previous 12 months. We compare time-series trends between MSM and heterosexual men to identify shifts in condom use. Figure A3.14 presents these changes. In the periods preceding PrEP's introduction (2008–2010), MSM were twice as likely as heterosexual men to report condom use. However, after 2012, the proportion of MSM not using condoms increased from 23% to 50% by 2016, while the statistic for heterosexual men remained stable at 40%. Notably, the 27 pp decline in condom use among MSM exceeds the estimated proportion of PrEP users, suggesting that the rise in risky sexual behavior

was a community-wide phenomenon rather than one confined to PrEP users alone.

8 Discussion

This paper advances our understanding of PrEP's real-world effectiveness and its potential in curbing the HIV epidemic. First, by exploiting geographic variation in male same-sex partnerships, we provide causal estimates of PrEP's impact: for every 28 additional PrEP users, one HIV diagnosis is averted. Second, we explore why aggregate HIV incidence has not fallen more dramatically despite PrEP's near-perfect clinical efficacy. While PrEP uptake is high among White MSM, the national plateau in HIV incidence is driven primarily by diagnoses among Black MSM, who underutilize PrEP relative to their risk. This pattern mirrors broader racial disparities in preventive care. Finally, we present evidence of a sharp decline in condom use among MSM that exceeds the proportion of PrEP users, which may undermine PrEP's population-level impact. Our findings highlight the importance of addressing both access barriers and behavioral responses to maximize PrEP's public health impact.

The HIV epidemic has claimed over 700,000 lives in the U.S., and federal and local governments spend billions annually in programs such as the Ryan White CARE Act and the Ending the HIV Epidemic by 2030 initiative. Since 2012, expanding PrEP access has been a cornerstone of these efforts. Yet, despite substantial investments, progress in reducing HIV incidence has stalled. With nearly universal awareness of PrEP, it is unlikely that traditional awareness campaigns alone will suffice. Our findings suggest that behavioral responses could erode PrEP's clinical benefits if left unaddressed.

Broadly, a complex policy trade-off exists between funding HIV treatment and expanding PrEP access. For individuals living with HIV, antiretroviral therapy can reduce viral loads to undetectable levels, effectively eliminating the risk of transmission. Consequently, directing resources toward diagnosing and treating HIV-positive individuals can be more cost-effective than targeting HIV-negative populations with PrEP. Shifting resources from treatment toward PrEP without careful calibration could inadvertently weaken prevention efforts. However, the persistent underutilization of PrEP among high-risk groups, notably Black MSM, suggests that a more targeted expansion could yield greater benefits. To illustrate, we conduct a back-of-the-envelope cost–benefit analysis.

Under the current regime, with 28 PrEP users required to avert one HIV diagnosis, and assuming an annual PrEP cost of $10,500 per individual, the cost to avert one infection is $294,000. Each averted infection not only spares an individual from a lifelong, costly

treatment regimen but also preserves quality-adjusted life years, estimated at a value of $326,500 (Schackman et al., 2015). Using these values, the current targeting regime is only marginally cost-effective. Consider instead a targeted regime among high-risk populations where only 10 additional PrEP users are needed to avert one HIV diagnosis. The cost per averted infection would then be $120,000, far below the lifetime cost of HIV treatment. This estimate is likely conservative, given that nearly one in two Black MSM face a lifetime risk of HIV.

Finally, legal challenges such as *Braidwood v. Becerra* threaten federal support that has been crucial in ensuring this "miracle drug" reaches at-risk populations. Over the past decade, PrEP has represented a medical breakthrough in HIV prevention, but our analysis underscores that the benefits of expanding PrEP access has potential to exceed clinical efficacy if adverse behavioral responses and utilization disparities are managed. In light of these findings, policymakers face a challenge: how to design and implement regulations that protect the gains achieved through decades of investment in HIV prevention and adapt to emerging legal and behavioral hurdles. The economic and public health stakes are high.

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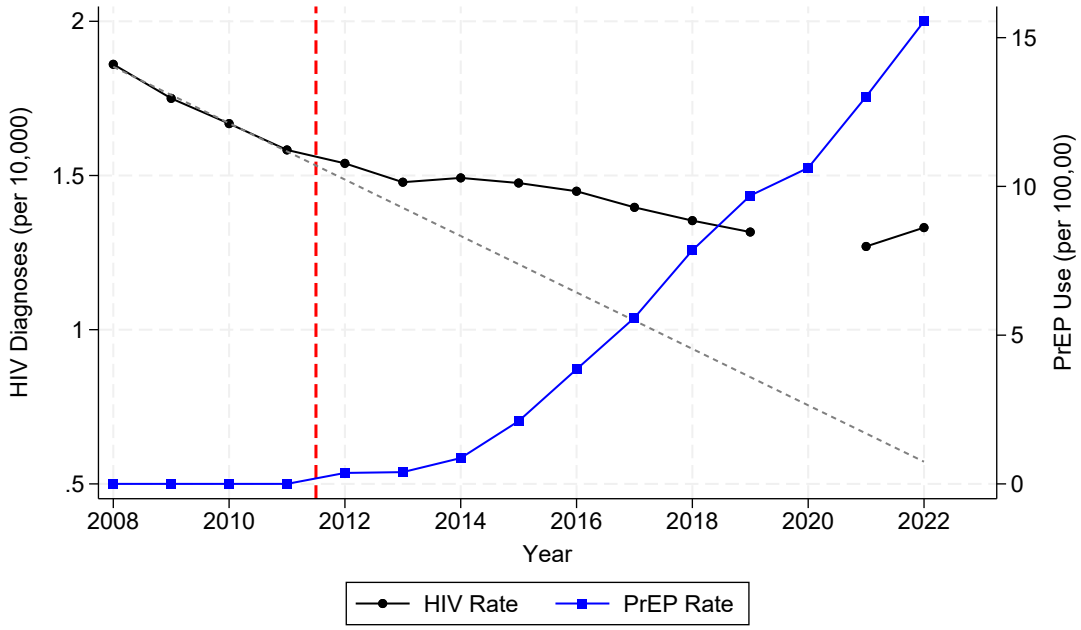
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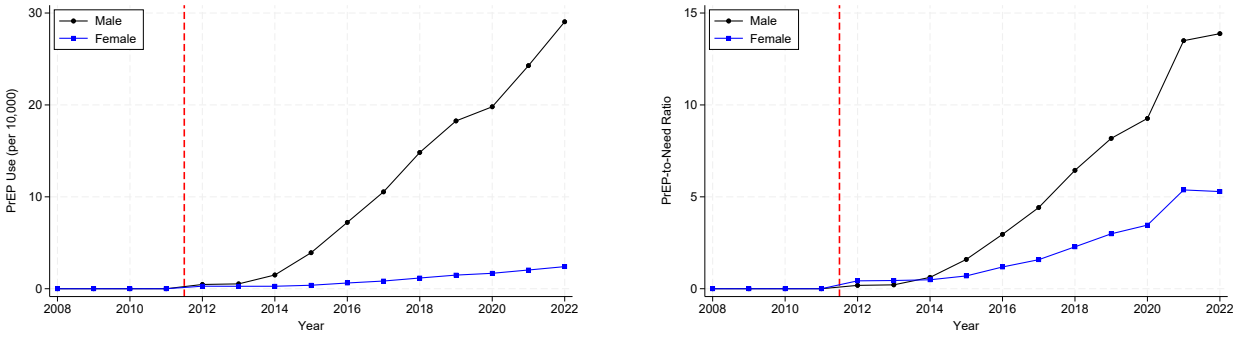
Figure 1: HIV Diagnosis and PrEP Usage Rates Over Time



Note: This figure plots the annual PrEP usage rate, defined as the number of PrEP users per 10,000 population, as blue squares (right y-axis). The figure also plots the annual HIV diagnosis rate, defined as the number of HIV diagnoses per 10,000 population, as black circles (left y-axis). The dashed gray line is a linear extrapolation of the HIV diagnosis rate based on the four years before PrEP was introduced. The introduction of PrEP is indicated by the vertical dashed red line.

Tables and Figures

Figure 2: PrEP Take-up Over Time, by Sex

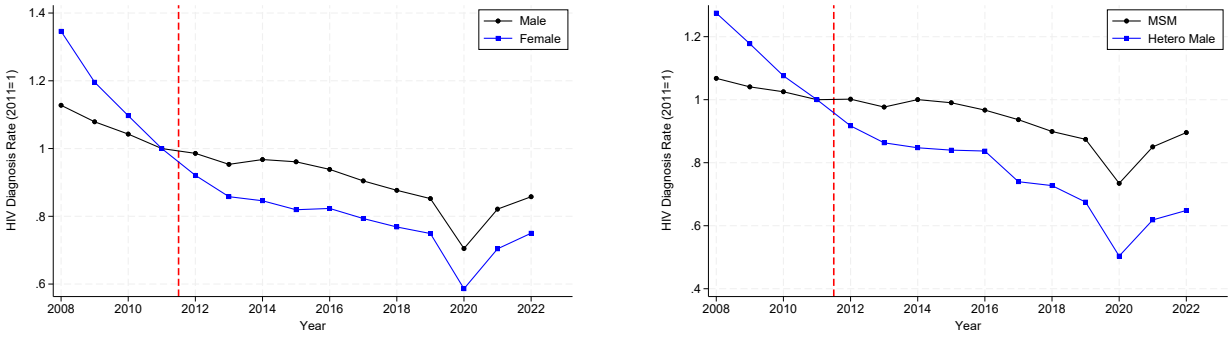


(a) PrEP Usage Rate

(b) PrEP-to-Need Ratio

Note: This figure plots two measures of PrEP uptake. Panel (a) displays the annual PrEP usage rate, defined as the number of PrEP users per 10,000 population. Panel (b) displays the PrEP-to-Need ratio, defined as the number of PrEP users divided by the previous year's number of HIV diagnoses. Both panels plot men as black circles and women as blue squares. The introduction of PrEP is indicated by the vertical dashed red lines.

Figure 3: HIV Diagnoses Over Time

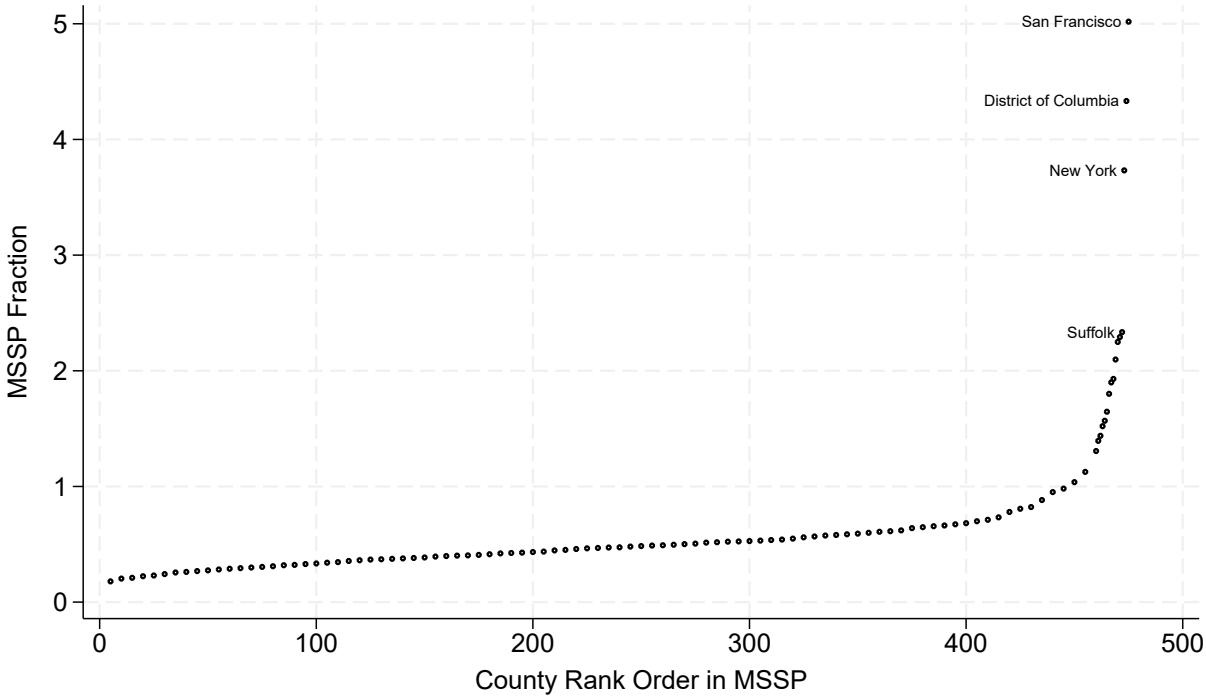


(a) By Sex

(b) Male Only - By Sexual Orientation

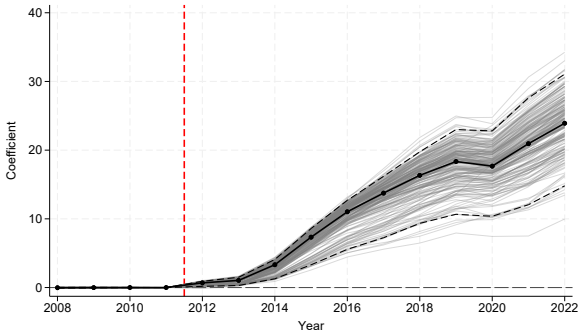
Note: These figures plot the annual HIV diagnosis rate by sex (panel (a)) and MSM/heterosexual men (panel (b)). In each panel, rates are normalized to one in 2011. Black circles represent men and MSM in panels (a) and (b), respectively, while blue squares represent women and heterosexual men. The introduction of PrEP is indicated by the vertical dashed red lines.

Figure 4: County Rank Order in Terms of MSSP

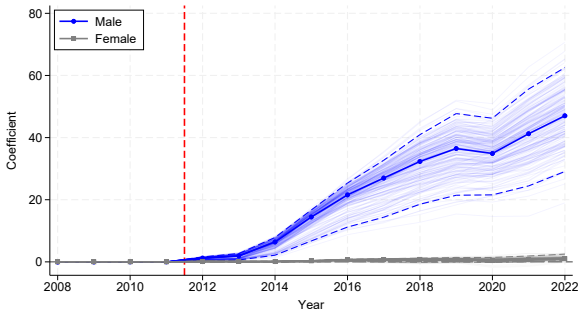


Note: This figure plots the share of MSSP in each county of our sample against the county's MSSP rank order, with one being the county with the lowest MSSP share. The figure only plots every fifth county (until the end of the sample) to enhance visibility.

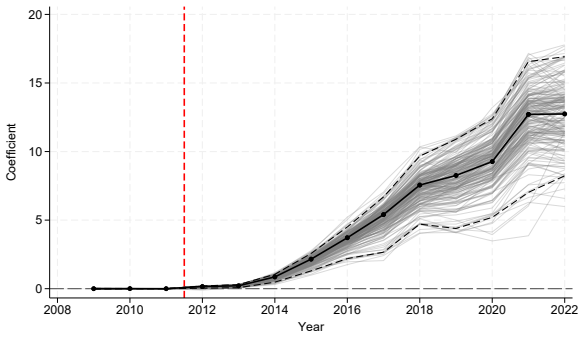
Figure 5: Synthetic Event Study Regression Results: PrEP Usage Rate and PrEP-to-Need Ratio



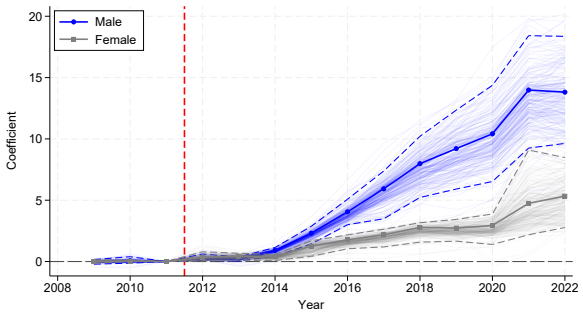
(a) PrEP Usage Rate



(b) PrEP Usage Rate by Sex



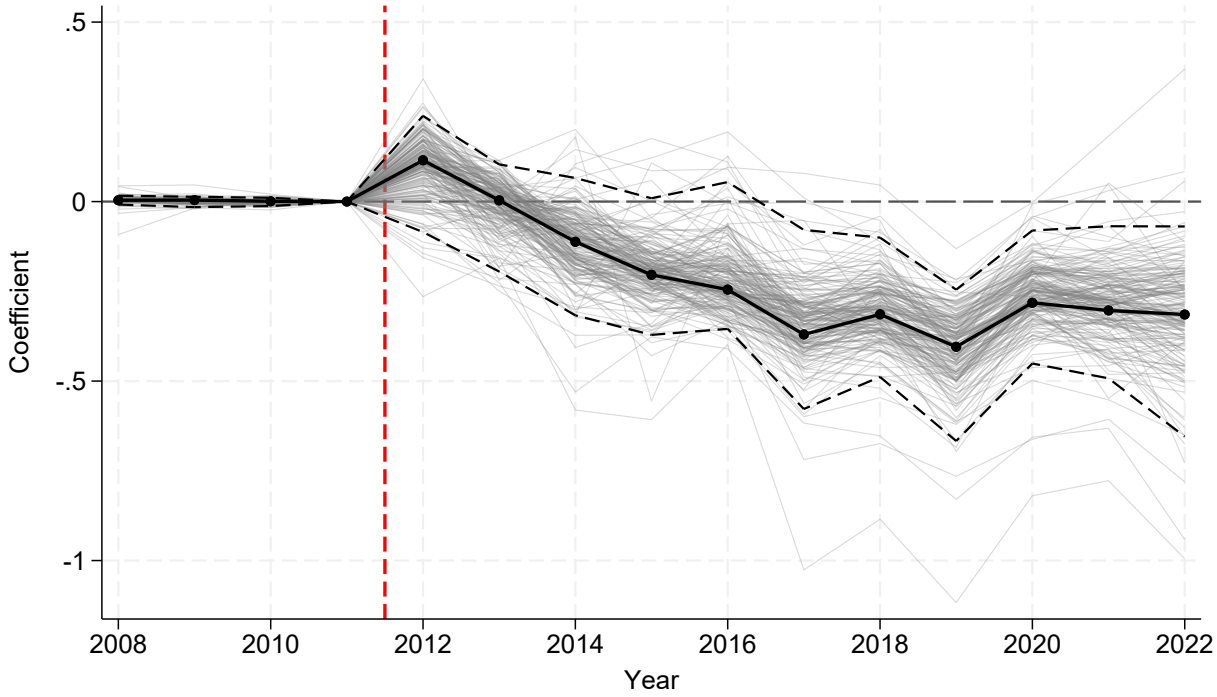
(c) PrEP-to-Need Ratio



(d) PrEP-to-Need Ratio by Sex

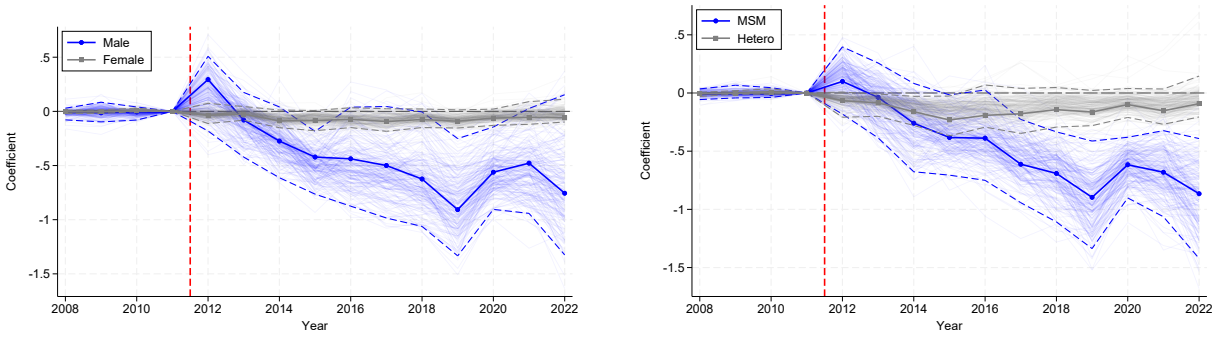
Note: This figure shows the synthetic event study regression results for various PrEP-related outcome variables. The aggregate PrEP usage rate, PrEP usage rate by sex, PNR, and PNR by sex are shown in panels (a)-(d), respectively. Point estimates are shown as black circles in panels (a) and (c), and blue circles for men and gray squares for women in panels (b) and (d). In each panel, the dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines.

Figure 6: Synthetic Event Study Regression Results: HIV Diagnosis Rate



Note: This figure shows the synthetic event study regression results for the HIV diagnosis rate. Point estimates are shown as black circles. The dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red line.

Figure 7: Synthetic Event Study Regression Results: HIV Diagnosis Rate by Sex and Sexual Orientation

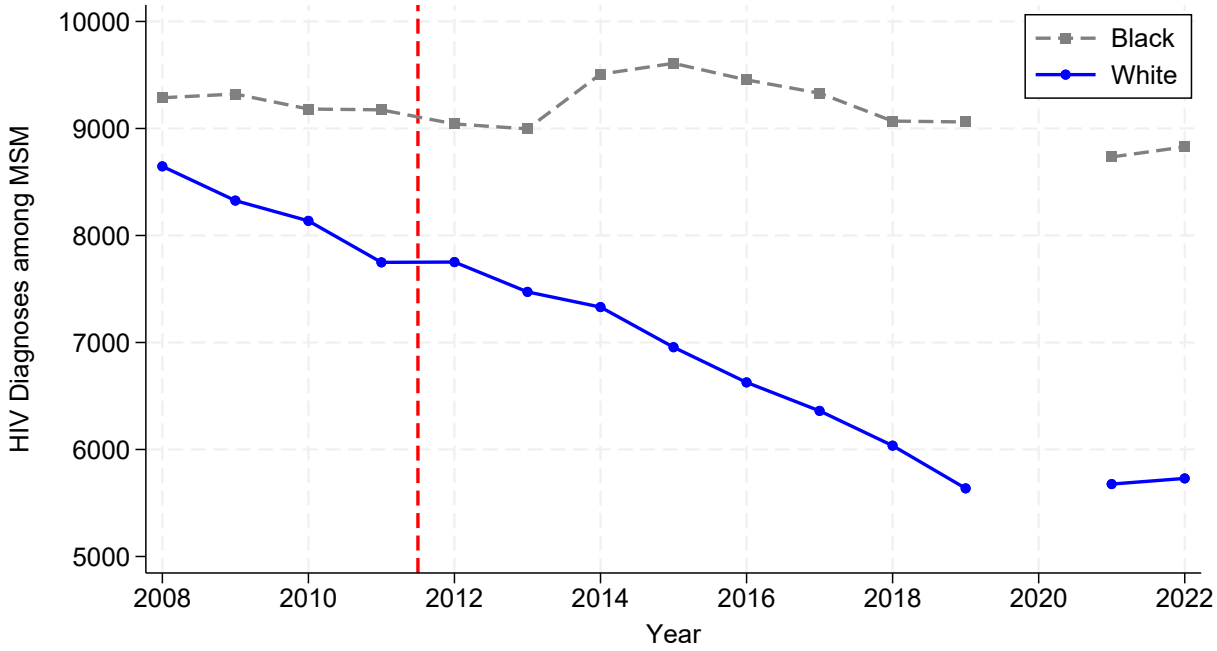


(a) HIV Diagnosis Rate by Sex

(b) Male HIV Diagnoses by Sexual Orientation

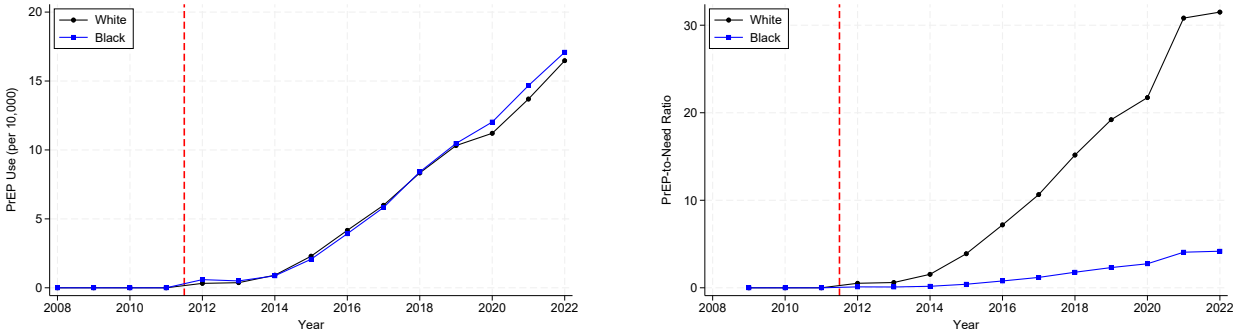
Note: This figure shows the synthetic event study regression results for sex-specific HIV diagnoses in panel (a) and male HIV diagnoses broken down by transmission category in panel (b). The transmission categories included in panel (b) are heterosexual contact and homosexual contact. Point estimates are shown as blue circles for males in panels (a) and MSM in panel (b). Point estimates are shown as gray squares for women in panels (a) and heterosexual men in panel (b). In each panel, the dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines.

Figure 8: MSM HIV Cases Over Time, by Race



Note: This figure plots the annual number of HIV diagnoses for White and Black MSM as blue circles and gray squares, respectively. The introduction of PrEP is indicated by the vertical dashed red line. We omit the values in 2020 due to unusual values resulting from the COVID-19 pandemic.

Figure 9: PrEP Usage Rate and PrEP-to-Need Ratio Over Time, by Race

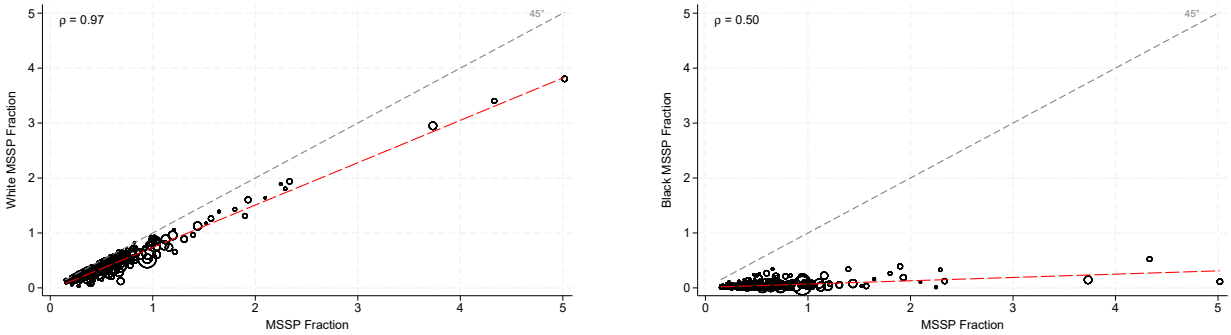


(a) PrEP Usage Rate

(b) PrEP-to-Need Ratio

Note: These figures show various measures of PrEP uptake over time by race Panel (a) plots the annual PrEP usage rate, while panel (b) plots the PrEP-to-Need ratio. In each panel, Whites are shown as black circles and Blacks are shown as blue squares. The introduction of PrEP is indicated by the vertical dashed red lines.

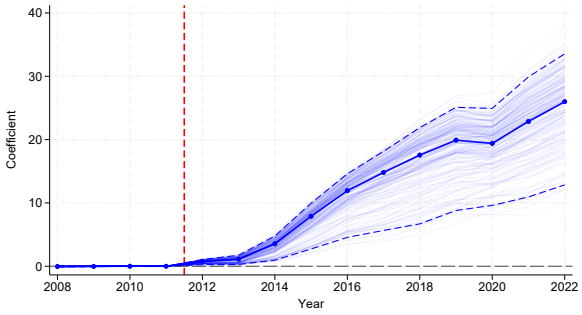
Figure 10: Overall Versus Race-Specific MSSP Share Correlations



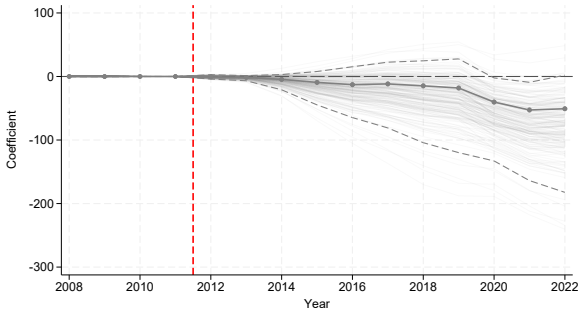
(a) White (b) Black

Note: This figure shows scatter plots of race-specific MSSP shares versus the aggregate MSSP share. Each county is represented by a black circle. The aggregate MSSP share is shown on the x-axis of each figure, while the White-specific and Black-specific MSSP shares are shown on the y-axis of panel (a) and (b), respectively. The line of best fit are indicated by dashed red lines in each sub-figure, and the 45 degree line is indicated by dotted gray lines in each sub-figure. Correlation coefficients are displayed in the top-left corner of each sub-figure.

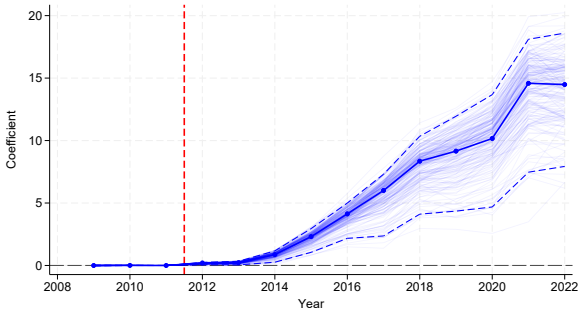
Figure 11: Synthetic Event Study Regression Results: PrEP Usage Rate and PrEP-to-Need Ratio by Race-Specific Treatment



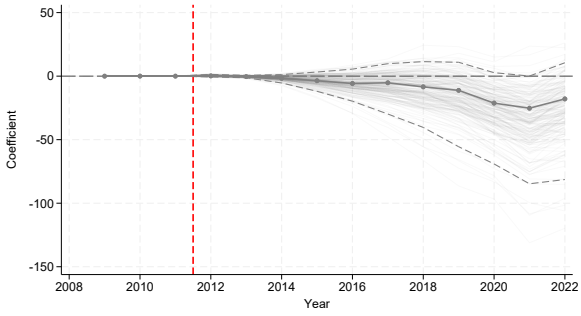
(a) PrEP Usage Rate, White MSSP



(b) PrEP Usage Rate, Black MSSP



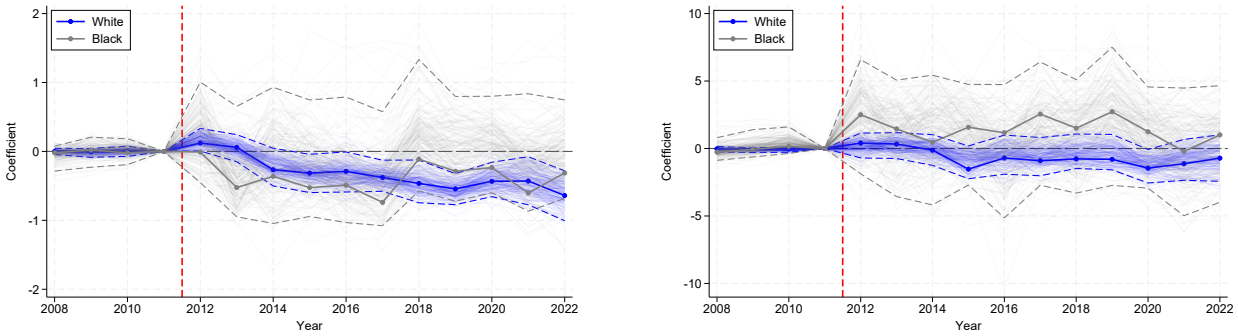
(c) PrEP-to-Need, White MSSP



(d) PrEP-to-Need, Black MSSP

Note: This figure shows the synthetic event study regression results for the PrEP usage rate (top row) and PNR (bottom row). The left panels use the White-specific MSSP share as the independent variable, while the right panels use the Black-specific MSSP share. In each panel, the dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines.

Figure 12: Synthetic Event Study Regression Results: HIV Diagnosis Rate by Race



(a) White-Specific MSSP

(b) Black-Specific MSSP

Note: This figure shows the synthetic event study regression results for race-specific HIV diagnoses using race-specific treatment variables. The left panels use the White-specific MSSP share as the independent variable, while the right panels use the Black-specific MSSP share. In each panel, coefficients for Whites are shown as blue cirlces and coefficients for Blacks are shown as gray circles. The dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines.

Table 1: Descriptive Statistics

	Quartile of MSSP Share			
	(1)	(2)	(3)	(4)
Panel (a): Before PrEP				
HIV Diagnosis Rate	0.820	1.260	1.533	2.631
PrEP Usage Rate	0.000	0.000	0.000	0.000
Fraction Black	6.517	10.933	12.855	16.339
Fraction White	80.615	71.199	70.923	62.867
Fraction Latino	9.370	12.582	10.108	13.209
MSSP Share	0.281	0.416	0.532	0.980
Population	165,845	273,544	345,330	675,866
Number of Counties	119	119	119	118
Observations	476	476	476	472
Panel (b): After PrEP				
HIV Diagnosis Rate	0.820	1.135	1.291	1.949
PrEP Usage Rate	2.994	3.302	4.130	8.827
Fraction Black	7.082	11.462	13.696	16.611
Fraction White	77.361	67.402	66.815	59.383
Fraction Latino	11.140	14.733	11.970	14.927
MSSP Share	0.281	0.416	0.532	0.980
Population	181,371	295,396	374,444	729,036
Number of Counties	119	119	119	118
Observations	1,309	1,309	1,309	1,298

Note: This table presents summary statistics for several key variables. In each panel, the table is broken down by quartile of the MSSP share. Panel (a) presents summary statistics from 2008-2011, the four years before PrEP's introduction. Panel (b) presents the same statistics from 2012-2022, the period after PrEP's introduction. The HIV diagnosis and PrEP usage rates variables are defined per 10,000 population. The fractions of Black, White, and Latino, as well as the MSSP share, are measured on a 0-100 scale.

A Appendix

A.1 Multi-Type Model of HIV Transmission

This section outlines an augmented Susceptible-Infected-Removed (SIR) model to capture HIV dynamics across two subpopulations ("types") with differing degrees of HIV risk, PrEP adoption, and homophily in their sexual activity. Consider two types indexed by $i \in \{1, 2\}$.

$$S_t^i, \quad I_t^i, \quad R_t^i$$

denote the proportions of susceptible, infected, and removed individuals within group i at time t, respectively. Individuals in group i contact individuals in group j at a rate governed by the mixing parameter $\alpha_{i,j}$, where $\alpha_{i,1}+\alpha_{i,2} = 1$. An infected individual of type j transmits HIV to a susceptible of type i with per-contact probability $\beta_{i,j}$. Let γ_i denote the removal rate for group i. In the absence of PrEP, the two-group SIR dynamics are:

$$\begin{aligned}
\frac{dS_t^i}{dt} &= -S_t^i \Big[\alpha_{i,1}\,\beta_{i,1}\,I_t^1 + \alpha_{i,2}\,\beta_{i,2}\,I_t^2\Big] \\
\frac{dI_t^i}{dt} &= S_t^i \Big[\alpha_{i,1}\,\beta_{i,1}\,I_t^1 + \alpha_{i,2}\,\beta_{i,2}\,I_t^2\Big] - \gamma_i\,I_t^i \\
\frac{dR_t^i}{dt} &= \gamma_i\,I_t^i
\end{aligned}$$

Utility Maximization Individuals derive utility from sexual activity but face the risk of HIV infection. Each individual chooses a binary decision $a \in \{0, 1\}$ on whether to adopt PrEP and a decision $r \geq 0$ representing the intensity of sexual risk-taking. Let $u(r)$ denote the utility from sexual activity that is increasing in r, $c_i \geq 0$ be the cost of adopting PrEP for an individual in group i, $\lambda > 0$ capture the disutility associated with HIV risk, β_0 be the baseline per-contact transmission probability, and $\theta \in [0, 1]$ be the clinical efficacy of PrEP. Then, the effective per-contact transmission probability is:

$$\beta(a) = \begin{cases} \beta_0, & \text{if } a = 0 \\ \beta_0(1-\theta), & \text{if } a = 1 \end{cases}$$

The individual's utility is:

$$U(r, a) = u(r) - c_i\,a - \lambda\,\beta(a)\,r$$

The first-order condition with respect to r is:

$$u'(r^*(a)) = \lambda\,\beta(a).$$

Since $\beta(1) < \beta(0)$ when $\theta > 0$, individuals who adopt PrEP will choose a higher optimal r than those who do not, reflecting sexual risk compensation associated with PrEP.

Behavioral Spillovers As PrEP adoption becomes more common, norms in sexual activity may shift such that even individuals who do not adopt PrEP increase their sexual risk-taking. We capture this by introducing a spillover multiplier $\phi(p_t) \geq 1$, which is an increasing function of the population-level PrEP uptake p_t.

Let p_t^i denote the fraction of susceptible individuals in group i who adopt PrEP at time t. Then, the overall effective per-contact transmission probability experienced by a susceptible individual in group i when encountering an infected individual from group j is an average of the risks for PrEP and non-PrEP users:

$$\beta_{i,j}^* = \beta_{i,j}\Big[(1 - p_t^i) + \phi\,(1 - \theta)\,p_t^i\Big]$$

Augmented SIR Equations Substituting the endogenized transmission probability into the SIR dynamics, the differential equations for each group i are:

$$\begin{aligned}
\frac{dS_t^i}{dt} &= -S_t^i\Big[\alpha_{i,1}\,\beta_{i,1}^*\,I_t^1 + \alpha_{i,2}\,\beta_{i,2}^*\,I_t^2\Big],\\
\frac{dI_t^i}{dt} &= S_t^i\Big[\alpha_{i,1}\,\beta_{i,1}^*\,I_t^1 + \alpha_{i,2}\,\beta_{i,2}^*\,I_t^2\Big] - \gamma_i\,I_t^i,\\
\frac{dR_t^i}{dt} &= \gamma_i\,I_t^i,
\end{aligned}$$

These equations capture the joint effects of heterogeneous PrEP uptake, individual risk-taking decisions, and normative spillovers that elevate risk behavior across the population. In particular, even if one group has lower PrEP uptake (due to higher costs c_i or access barriers), the spillover effects through ϕ may still raise the overall effective transmission rate.

This augmented framework allows each group i to have its own PrEP uptake path p_t^i. The reduction in transmission risk is determined by the product $\phi_i\,p_t^i$ (capturing both behavioral adjustments and uptake) rather than simply by $\theta\,p_t^i$. Consequently, if group 1 exhibits a lower PrEP uptake p_t^1, then the real-world effectiveness of PrEP in that group will be substantially diminished compared to group 2. This disparity may allow group 1 to persist as a reservoir for the epidemic.

Implications for Disparities One insight from considering multiple subpopulations is that infections in one group will not remain confined there as long as there is any cross-group mixing. Even if group 2 achieves a higher PrEP uptake p_t^2, that group can still experience new infections if there is sufficient interaction with group 1, where lower PrEP uptake fails to suppress transmission. In the extreme case of very strong homophily ($\alpha_{1,2} \approx 0$), the epidemic in group 1 might be largely contained within that group; however, even small amounts of cross-group interaction can lead to spillover infections. This highlights the policy importance of targeting high-risk, low-uptake subpopulations for PrEP expansion, as it benefits not just that subpopulation but also the broader population.

A.2 Evidence on Identifying Assumptions

Our identifying assumption is that, in the absence of PrEP, trends in HIV rates within each county would have been parallel between real and synthetic counties. As discussed in Section 4, this implies that $\ddot{y}_{ct} = 0$ in the absence of the introduction of PrEP. We provide two indirect pieces of evidence in support of this assumption.

Placebo Tests First, we conduct traditional placebo tests. We do this by considering the effect of the introduction of PrEP on HIV diagnoses groups who had little to no PrEP takeup in practice. Specifically, we consider women and heterosexual men. We note that, even in the absence of a direct effect of PrEP on HIV among these groups, there could still be spillovers which would reduce HIV transmission. The results of this exercise are discussed in Section 5, and displayed graphically in Figure 7. That we see no effects for women (panel (a)) or heterosexual men (panel (b)) is supportive of our identifying assumption. That groups who had little PrEP takeup did not see declines in HIV diagnoses following PrEPs introduction suggests that, in the absence of PrEP, neither would the groups who were the primary users of PrEP.

Null Effects in Counties with Similar Synthetic and Actual MSSP Shares Our identifying assumption concerns counterfactuals in which PrEP was never introduced. We investigate counties with $\ddot{MSSP}_c \approx 0$ as an analog of this. The idea is that, if the synthetic and actual MSSP are similar, then there should be no differential PrEP takeup and therefore no effect on downstream outcomes such as HIV. Specifically, we do the following:

1. Divide counties into 10 deciles in terms of $\ddot{MSSP}_c$. Recall that this variable is measuring the gap between actual MSSP and synthetic MSSP. High values of this variable are counties whose actual and synthetic HIV rates are similar, but their actual MSSP is higher than their synthetic.

2. Take the average of $\ddot{y_{ct}}$ each year within these deciles. We pool the 5th and 6th decile together as counties with $\ddot{MSSP}_c \approx 0$.

3. Plot the 1st, 5-6th, and 10th decile over time. The 1st decile represents counties who have less MSSP than their synthetic, so we expect to see less PrEP usage and therefore more HIV diagnoses. We expect to see the opposite for the 10th decile. Since the middle deciles have little difference in actual and synthetic MSSP, so we don't expect to see and differential PrEP usage, and therefore no differences in HIV diagnoses.

4. Repeat this process for our 200 bootstrapped samples to obtain confidence intervals.

We present the results of this exercise in Figures A3.8 and A3.9. Figure A3.8 shows the results for PrEP usage in the top row and PNR in the bottom row. In each row, the left-hand panel plots the pooled 5th and 6th decile, while the right-hand rows plot the 1st and 10th deciles. The left-hand panels reveal that, when $\ddot{MSSP}_c \approx 0$, there is essentially no difference in PrEP usage or PNR. This indicates that, in counties where the MSSP share is

similar, there is little differential PrEP usage. This is supportive of the idea that differences in MSSP share are the key driver in county-level variation in the number of PrEP users. While not a test of the identifying assumption, the right-hand panels show that PrEP usage and PNR are higher (lower) in areas with higher (lower) MSSP shares in the actual versus synthetic county. This is precisely what we expect, and is not surprising given the event study results.

We show the results for HIV diagnoses in Figure A3.9. Again, the left panel shows no evidence of changes in HIV diagnoses in counties with $\ddot{MSSP}_c \approx 0$, consistent with our identifying assumption. Panel (b) shows results that are directionally consistent with our hypothesis, although we note that the results are relatively noisy. That said, this figure utilized less variation in than our main results, and overall is supportive of our narrative.

A.3 Alternative Explanations

Changes in Injection Drug Use Although sexual contact is by far the most common method of transmitting HIV, injection drug use is another important mode of transmission. Our empirical strategy essentially compares counties against their synthetic counterparts which have similar HIV trajectories (by construction), but differ in terms of their MSSP shares. If counties with differing actual versus synthetic MSSP shares also differ in their injection drug use, this could bias our results.

Ideally, we would investigate this issue using information specifically on injection drug use. Unfortunately, this type of data is not readily available at the county level. Instead, we collect data on the rate of annual drug overdose deaths in each county of our sample from CDC WONDER from 2008 to 2022 (CDC, National Center for Health Statistics. National Vital Statistics, 2023). Rates of injection drug use are likely higher in counties with high rates of drug overdose deaths, so this is a reasonable proxy. We use the same weights that we computed matching on HIV trends in order to construct synthetic drug overdose rates for each county. Using these synthetic counties, we follow the same process as in our main analysis to examine how the introduction of PrEP affected drug overdose deaths. We present the results in Figure A3.7. Every single coefficient in this event study is statistically insignificant, indicating that counties whose synthetic counterpart had similar HIV trends but differing MSSP shares did not see any changes in drug overdose death rates after the introduction of PrEP. This suggests that our results are not being driven by a spurious correlation between MSSP shares and injection drug use.

Imperfect Measurement of Incidence Throughout this paper, we consider HIV diagnoses rates, which measure the rate of individuals newly *diagnosed* with HIV. However, what we really care about is HIV incidence rates, that is, the rate of new *cases* of HIV, regardless of whether the infected individual was diagnosed or not. Perfect data on incidence does not exist as there is no systematic, randomized testing in the population.

However, starting in 2017 the CDC began publishing HIV incidence estimates for a subset of the counties in our sample. We provide a scatter plot of this estimated incidence against diagnoses from 2017 to 2022 in Figure A3.10. This figure displays diagnoses on the x-axis

and estimated incidence on the y-axis. Blue circles are county-years with information on both diagnoses and incidence, while the red circles represent county-year with no incidence information available. As is clear from the figure, incidence estimates are generally missing for county-years with very few HIV diagnoses. However, the two series are highly correlated, with a correlation coefficient of 0.97. This is suggestive that, while our primary outcome variable is HIV diagnoses, we can safely generalize our results to HIV incidence.

We examine HIV incidence directly in our empirical framework in Figure A3.11. However, because the incidence data do not begin until 2017, we cannot match on pre-period incidence trends. Instead, we use the same weights we calculated for the HIV diagnosis rate. We then use those weights to construct synthetic controls for each counties HIV incidence rate.[16] Once we have synthetic HIV incidence rates, we can directly estimate equation 6 following the same process described in Section 4. The only difference is that we use 2017–the first year of data– as the omitted period. We then normalize this to equal the value of the 2017 interaction from the HIV diagnosis rate event study. These results are shown in Figure A3.11. The baseline estimates using the HIV diagnosis rate are shown in black. These are the same estimates as in Figure 6, and are shown for comparison. The results for the HIV incidence rate are shown as blue squares. We obtain 95 percent confidence intervals by bootstrapping, and show the confidence interval for each outcome in the color corresponding to the point estimates.[17] Overall, the pattern of results is nearly identical, suggesting that differences between reported diagnoses and underlying incidence are not driving our results.

PrEP-Induced Changes in HIV Testing As discussed in Section 5, regular HIV testing (usually every three months) is a requirement to obtain a PrEP prescription. Thus, one may be concerned that PrEP's introduction could lead to large increases in HIV testing, which could lead to more HIV diagnoses even in the absence of any changes in underlying HIV incidence. While we did not see any evidence that HIV diagnoses deviate from estimates of HIV incidence in the previous section, we investigate this possibility in this section.

We collect data on the annual rate of HIV testing at the state-by-year-by-sex level from the Behavioral Risk Factor Surveillance System (BRFSS) dataset from 2008 to 2022 CDC (2006).[18] We first examine how HIV testing has changed over time in Figure A3.12. This figure plots the fraction of individuals who report having an HIV test in the 12 months prior to the interview date. We plot men as black circles and women as blue squares. This figure reveals two interesting facts. First, despite men having significantly higher HIV risk, there do not appear to be any systematic differences in HIV testing behavior by sex. Second, there is no obvious increase in testing that occurs after 2012, the year that PrEP was introduced, for either men or women. However, the lack of an aggregate response does not necessarily preclude an increase in testing in the areas that saw large increases in PrEP takeup. In order to investigate this, we estimate a triple differences event study, comparing men and

[16]The incidence data is missing for many of the counties in our full sample. In order to apply the weights obtained from the diagnosis rate, we regress HIV incidence on the HIV diagnosis rate and use the estimates of this regression to predict HIV incidence for the missing observations for 2017 to 2022.

[17]We do not display every iteration as in Figure 6 to keep the figure legible.

[18]County identifiers are unavailable in the BRFSS data.

women in states with higher and lower MSSP shares before and after the introduction of PrEP.[19] The idea behind the triple difference is that men, who had higher rates of PrEP usage, should have increased their testing more than women if changes in testing behavior were driving our results. We present the event study coefficients in Figure A3.13. This figure reveals that there is essentially no difference over time in male versus female testing behavior in states with higher or lower MSSP shares. This suggests that the change in HIV diagnoses that we observed for men are not driven by differential testing behavior that led to more diagnoses with no underlying change in incidence. In results not presented here, we estimate difference-in-differences models separately for men and women, as well as pooled together, and find no evidence of changes in testing for any group.

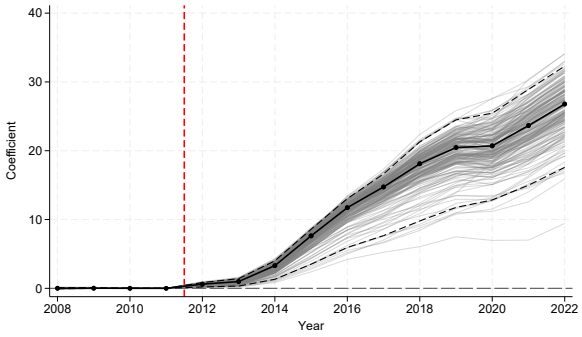
[19]We use state level data because we do not have any county information in the BRFSS.

Table A3.1: Selected Phase III and Phase IV Clinical Trials of PrEP

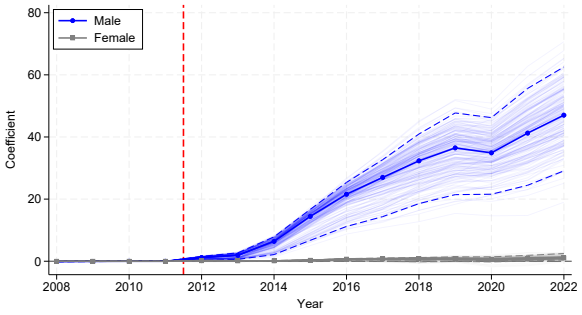
Study	**Population**	**Sample**
iPrEx (2010, Phase III)	MSM and transgender women (United States, Peru, Ecuador, Brazil, Thailand, South Africa)	2,499
Partners PrEP (2012, Phase III)	Heterosexual serodiscordant couples (Kenya, Uganda)	4,758
TDF2 (2012, Phase III)	Heterosexual men and women (Botswana)	1,219
Bangkok Tenofovir Study (2013, Phase III)	People who inject drugs (Thailand)	2,413
VOICE (2013, Phase IIb/III)	Women (Sub-Saharan Africa)	5,029
PROUD (2015, Phase III/IV)	MSM (United Kingdom)	544
IPERGAY (2015, Phase III)	MSM (France, Canada)	400
ASPIRE (2016, Phase III)	Women (Sub-Saharan Africa)	2,629
The Ring Study (2016, Phase III)	Women (Sub-Saharan Africa)	1,959
iPrEx OLE (2014, Phase IV)	MSM and transgender women (Global)	1,603
HOPE (2017, Phase IIIb)	Women (Sub-Saharan Africa)	1,456
DREAM (2018, Phase IIIb)	Women (Sub-Saharan Africa)	1,145
DISCOVER (2019, Phase III)	MSM and transgender women (North America, Europe)	5,387
HPTN 083 (2020, Phase IIb/III)	MSM and transgender women (Global; 21 countries)	4,570
HPTN 084 (2020, Phase III)	Cisgender women (Sub-Saharan Africa)	3,224

Note: This table presents clinical trials evaluating daily, on-demand, and long-acting PrEP regimens. Phases reflect regulatory stages of clinical development, from robust efficacy testing (Phase III) to post-marketing assessments (Phase IV). Sample sizes denote enrolled participants, although the final analyzed cohorts may be smaller due to attrition or protocol deviations. This list is non-exhaustive and focuses on major trials.

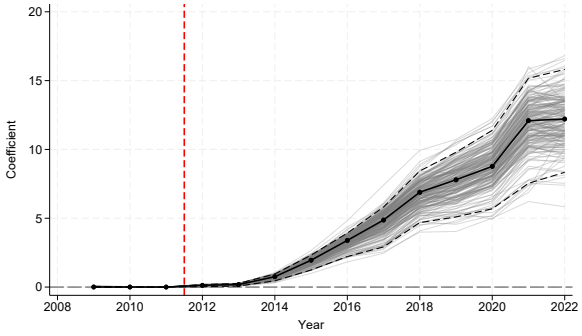
Figure A3.1: Synthetic Event Study Regression Results Keeping All Matches: PrEP Usage and PrEP-to-Need Ratio



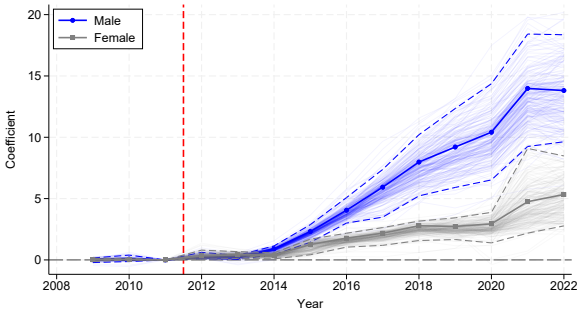
(a) PrEP Usage



(b) PrEP Usage by Sex



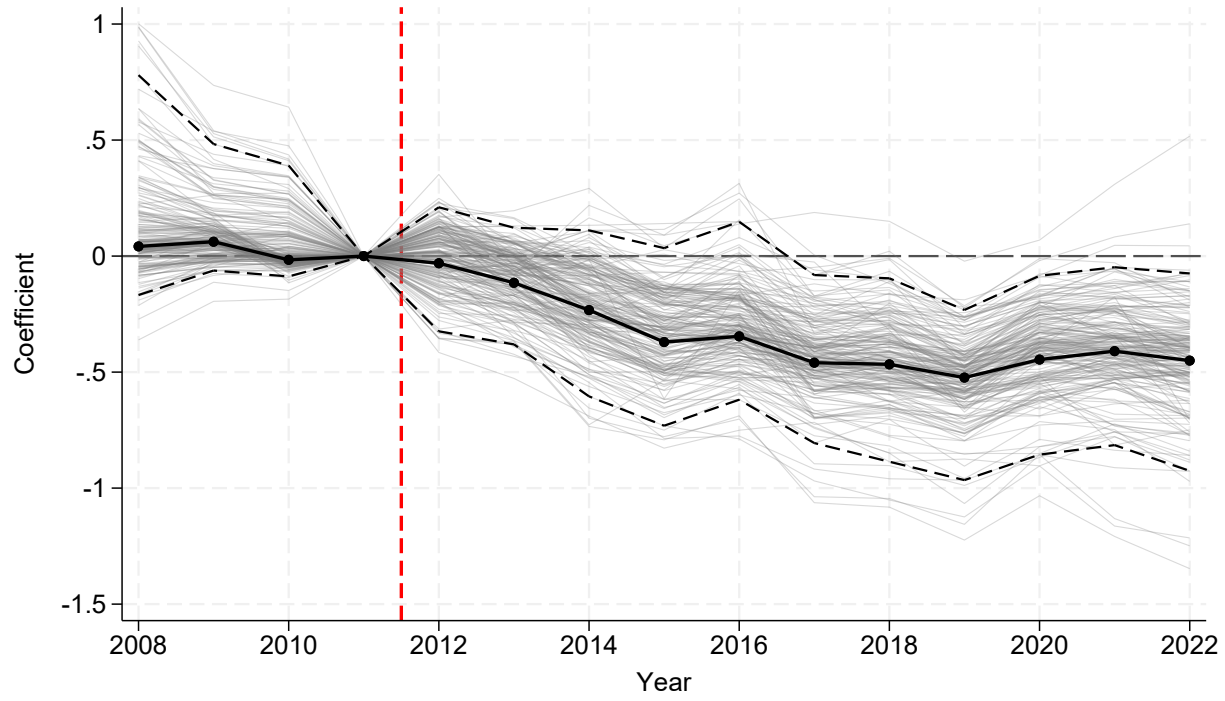
(c) PrEP-to-Need Ratio



(d) PrEP-to-Need Ratio by Sex

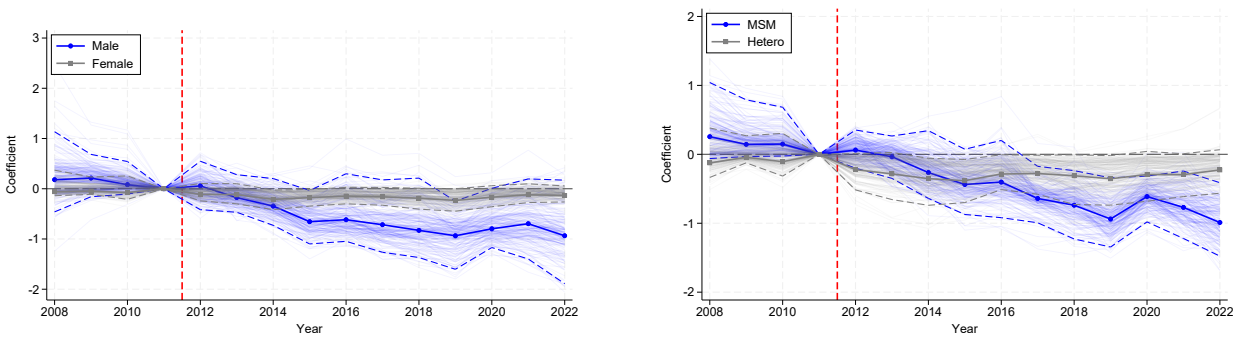
Note: This figure shows the synthetic event study regression results for various PrEP-related outcome variables. Aggregate PrEP usage, PrEP usage by sex, PNR, and PNR by sex are shown in panels (a)-(d), respectively. Point estimates are shown as black circles in panels (a) and (c), and blue circles for men and gray squares for women in panels (b) and (d). In each panel, the dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines. This figure differs from Figure 5 in that it does not drop counties without sufficiently close synthetic matches.

Figure A3.2: Synthetic Event Study Regression Results Keeping All Matches: HIV Diagnosis Rate



Note: This figure shows the synthetic event study regression results for the HIV diagnosis rate. Point estimates are shown as black circles. The dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red line. This figure differs from Figure 6 in that it does not drop counties without sufficiently close synthetic matches.

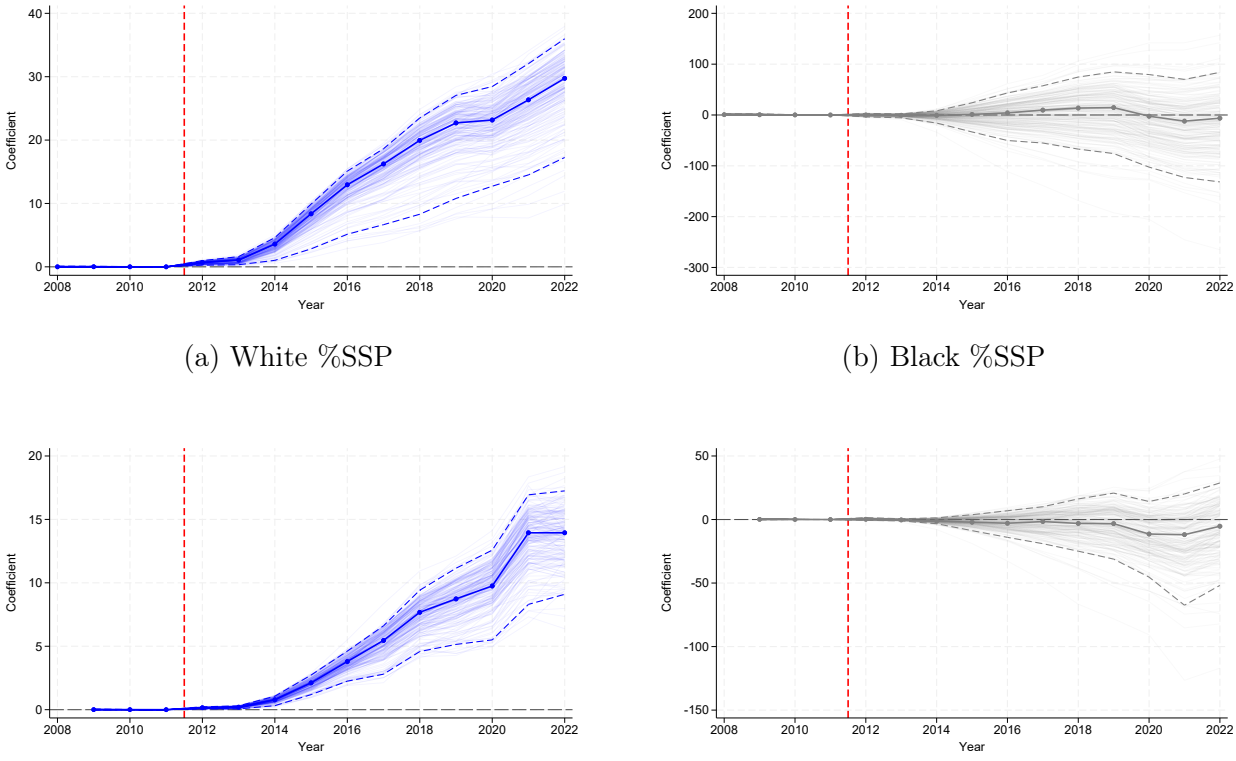
Figure A3.3: Synthetic Event Study Regression Results Keeping All Matches: HIV Diagnosis Rate by Sex and Sexual Orientation



(a) HIV Diagnosis Rate by Sex (b) Male HIV Diagnoses by Sexual Orientation

Note: This figure shows the synthetic event study regression results for sex-specific HIV diagnoses in panel (a) and male HIV diagnoses broken down by transmission category in panel (b). The transmission categories included in panel (b) are heterosexual contact and homosexual contact. Point estimates are shown as blue circles for males in panels (a) and MSM in panel (b). Point estimates are shown as gray squares for women in panels (a) and heterosexual men in panel (b). In each panel, the dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines. This figure differs from Figure 7 in that it does not drop counties without sufficiently close synthetic matches.

Figure A3.4: Synthetic Event Study Regression Results Keeping All Matches: PrEP Usage and PrEP-to-Need Ratio by Race-Specific Treatment



(a) White %SSP

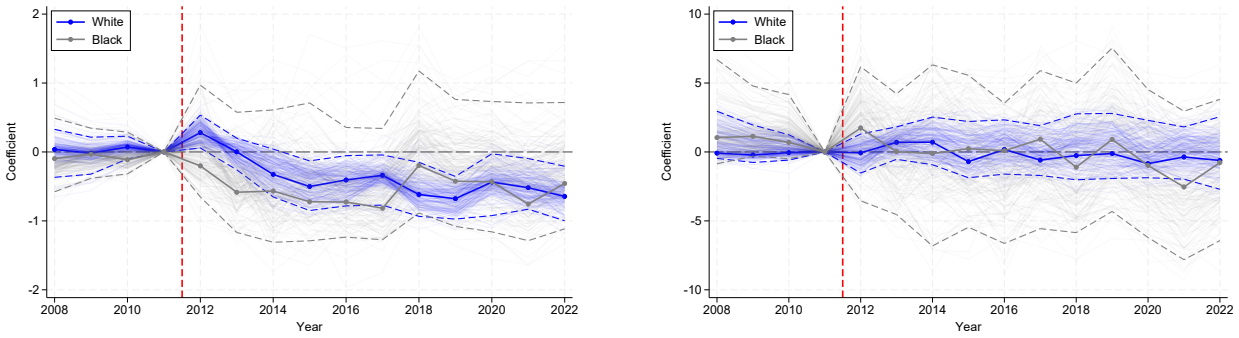
(b) Black %SSP

(c) White %SSP

(d) Black %SSP

Note: This figure shows the synthetic event study regression results for PrEP usage (top row) and PNR (bottom row). The left panels use the White-specific MSSP share as the independent variable, while the right panels use the Black-specific MSSP share. In each panel, the dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines. This figure differs from Figure A3.4 in that it does not drop counties without sufficiently close synthetic matches.

Figure A3.5: Synthetic Event Study Regression Results Keeping All Matches: HIV Diagnosis Rate by Race

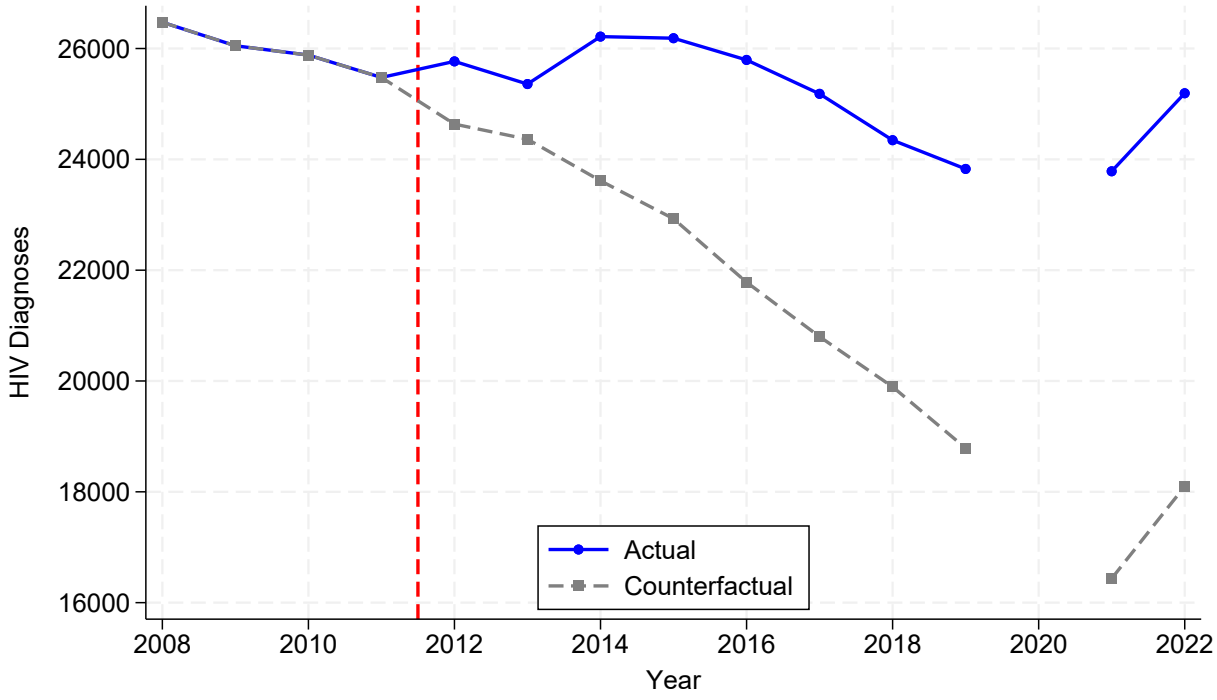


(a) White-Specific %SSP

(b) Black-Specific %SSP

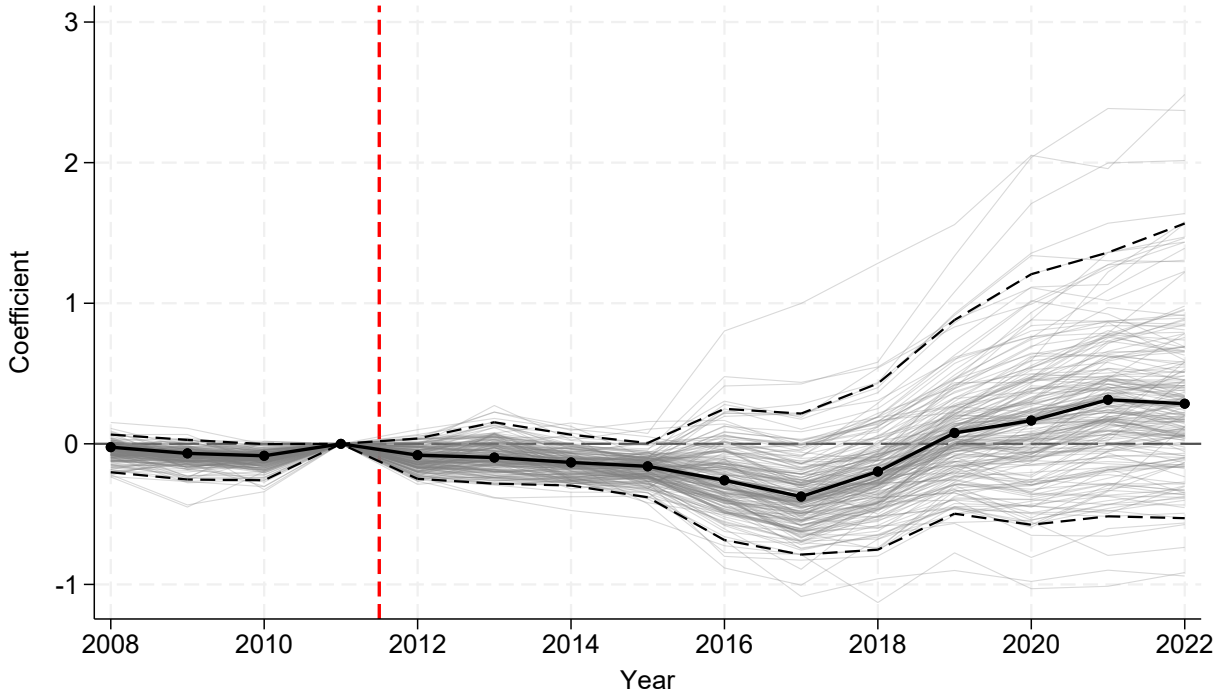
Note: This figure shows the synthetic event study regression results for race-specific HIV diagnoses using race-specific treatment variables. The left panels use the White-specific MSSP share as the independent variable, while the right panels use the Black-specific MSSP share. In each panel, coefficients for Whites are shown as blue cirlces and coefficients for Blacks are shown as gray circles. The dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red lines. This figure differs from Figure A3.5 in that it does not drop counties without sufficiently close synthetic matches.

Figure A3.6: Counterfactual MSM HIV Trends



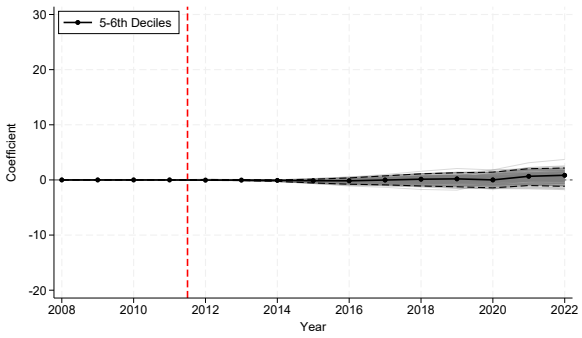
Note: This figure plots the annual number of HIV diagnoses among MSM as blue circles. The gray squares represent a counterfactual simulation in which the post-PrEP trends in HIV observed among White MSM are imposed on non-White MSM. In other words, this figure shows a counterfactual in which HIV trends among non-White MSM mirrored those of White MSM. We omit 2020 due to unusual values attributable to the COVID-19 pandemic.

Figure A3.7: Synthetic Event Study Regression Results: Drug Death Rate

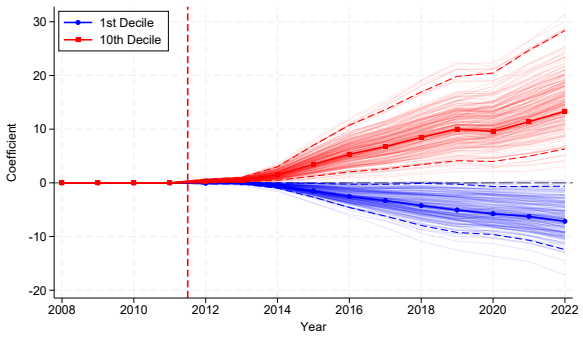


Note: This figure shows the synthetic event study regression results for the drug death rate. Point estimates are shown as black circles. The dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red line.

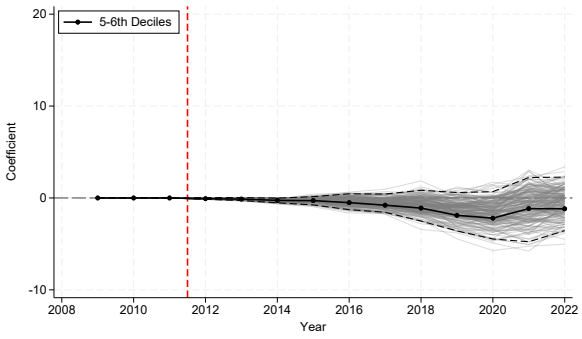
Figure A3.8: Identifying Assumption Test: PrEP Usage and PrEP-to-Need Ratio



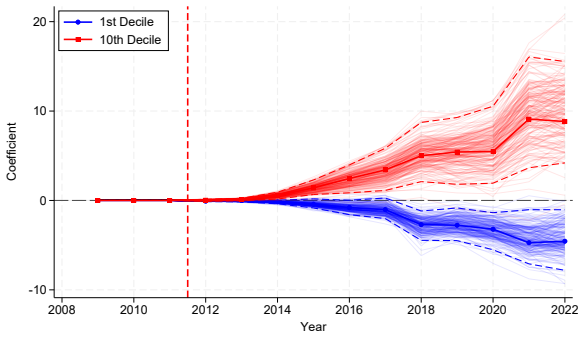
(a) PrEP Usage : $M\ddot{S}SP_c \approx 0$



(b) PrEP Usage: $M\ddot{S}SP_c \neq 0$



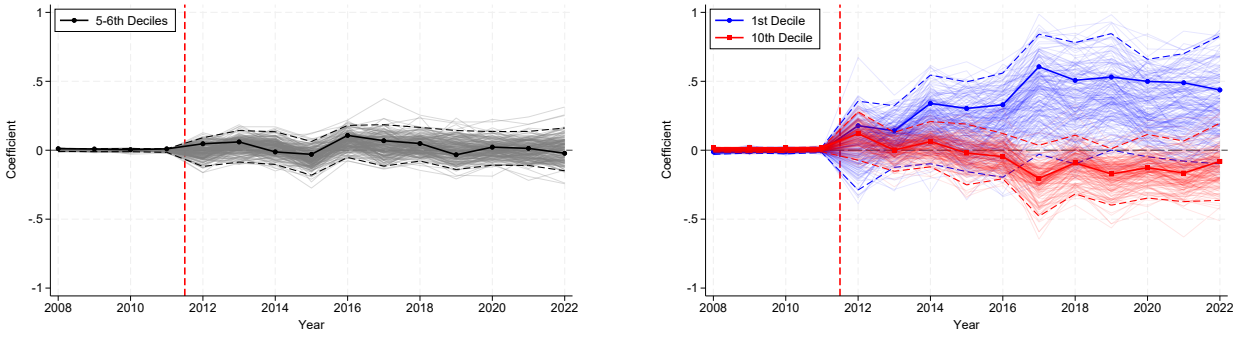
(c) PNR : $M\ddot{S}SP_c \approx 0$



(d) PNR: $M\ddot{S}SP_c \neq 0$

Note: These figures show the evolution of $\ddot{y_{ct}}$ over time for PrEP usage and PNR. The top row shows PrEP usage, while the bottom row shows PNR. The left panels restrict the sample to counties with $M\ddot{S}SP_c \approx 0$, specifically the 5th and 6th deciles. The right panels restrict the sample to counties with $M\ddot{S}SP_c$ far from 0, specifically the 1st and 10th deciles (blue circles and red squares, respectively). The dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red line.

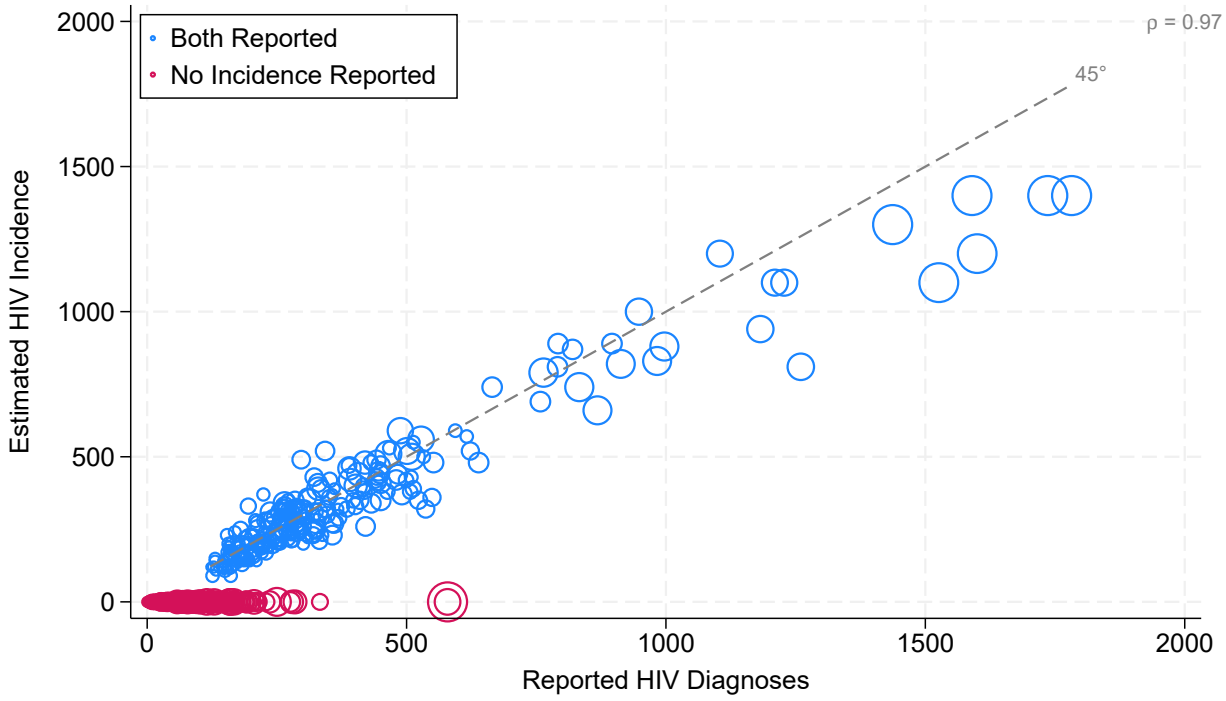
Figure A3.9: Identifying Assumption Test: HIV Diagnoses



(a) $M\ddot{S}SP_c \approx 0$ (b) $M\ddot{S}SP_c \neq 0$

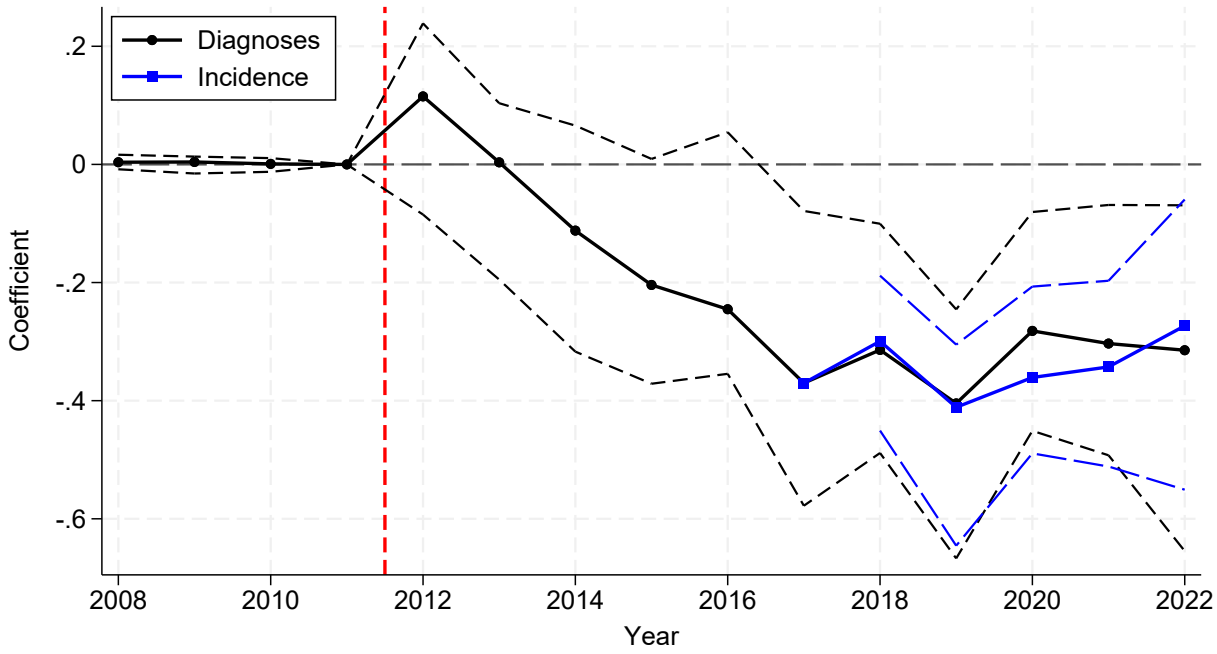
Note: These figures show the evolution of $\ddot{y_{ct}}$ over time HIV diagnoses. The left panel restricts the sample to counties with $M\ddot{S}SP_c \approx 0$, specifically the 5th and 6th deciles. The right panel restricts the sample to counties with $M\ddot{S}SP_c$ far from 0, specifically the 1st and 10th deciles (blue circles and red squares, respectively). The dashed lines are the 2.5th and 97.5th percentile of the distribution of bootstrapped estimates. The lightly colored, semi-transparent lines represent the set of estimates from a specific bootstrapped sample. The introduction of PrEP is indicated by the vertical dashed red line.

Figure A3.10: Scatter Plot: Estimated HIV Incidence Versus Diagnoses



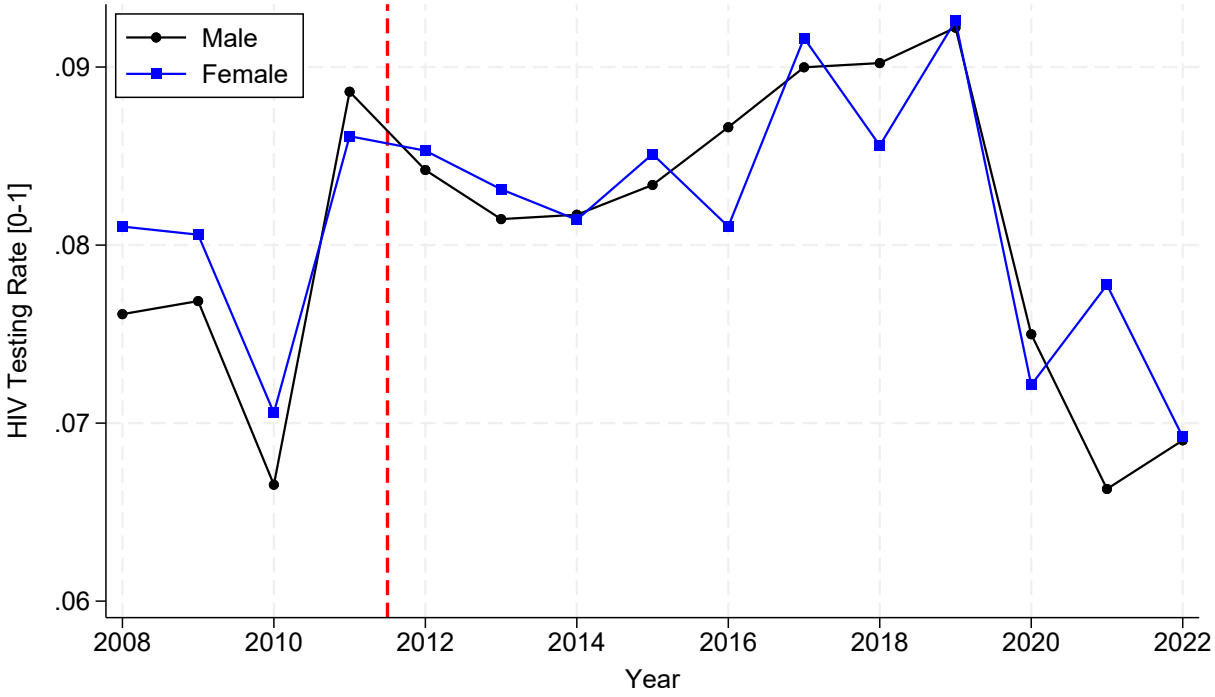
Note: This figure shows a scatter plot of the number of reported HIV diagnoses (x-axis) against the CDC's HIV incidence estimates (y-axis) at the county level from 2017-2022. Blue circles are county-years in which there is no missing data, while red circles are county years in which diagnoses are reported by incidence is not. The gray dashed line is the 45 degree line, and the correlation coefficient is displayed in the top right corner.

Figure A3.11: Synthetic Event Study Regression Results: HIV Diagnoses and Estimated HIV Incidence



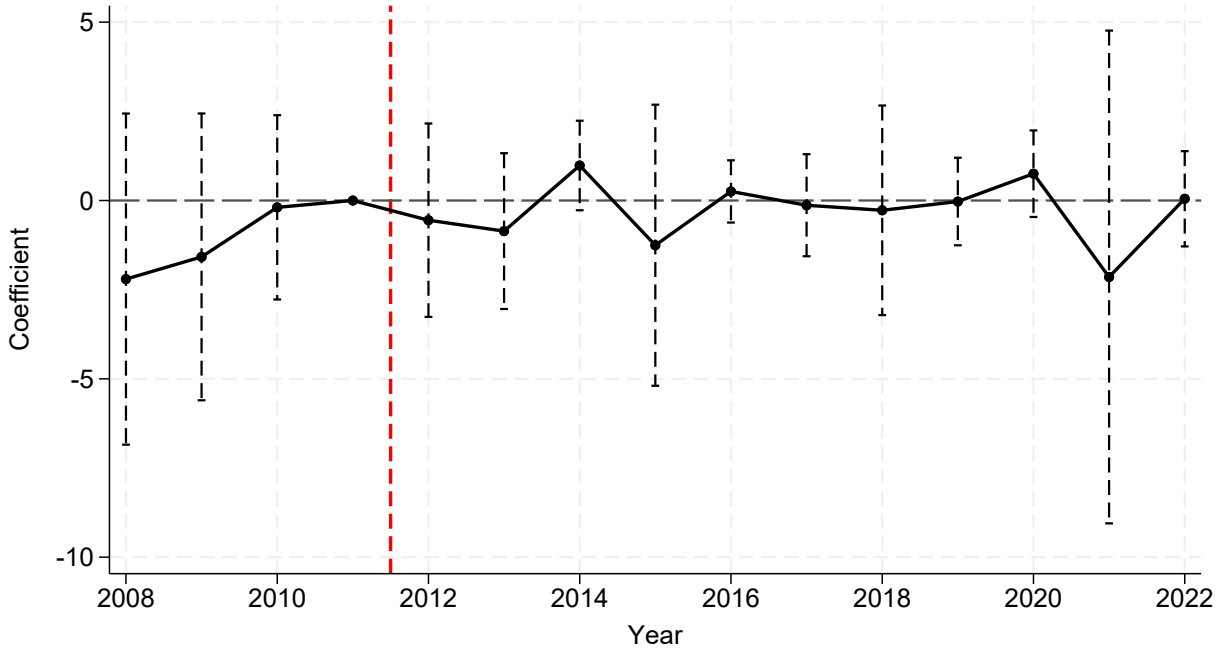
Note: This figure shows the synthetic event study coefficients and confidence intervals from Figure 6 in black, with the corresponding HIV incidence estimates in blue. The process for obtaining the HIV incidence coefficients is described in Appendix A.3. The introduction of PrEP is indicated by the vertical dashed red line.

Figure A3.12: HIV Testing Rate, by Sex



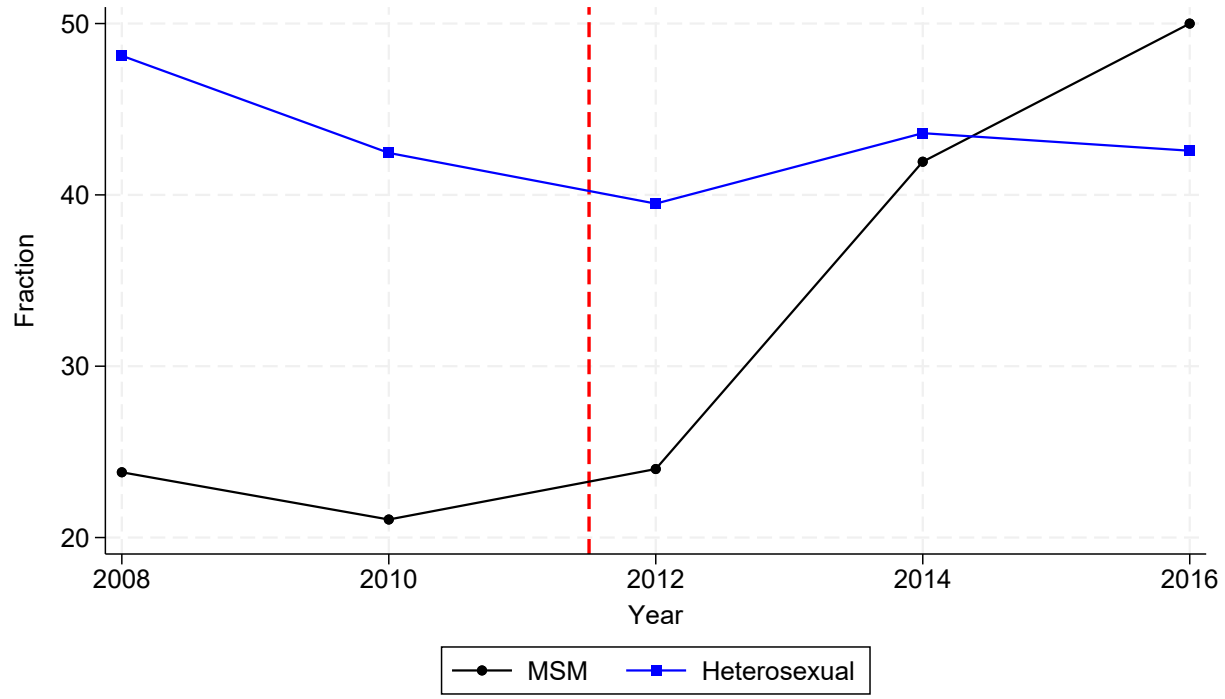
Note: This figure displays estimates of the annual rate of HIV testing on a 0-1 scale for men (black circles) and women (blue squares) using data from the BRFSS. The introduction of PrEP is indicated by the vertical dashed red line.

Figure A3.13: Triple Differences Event Study Results: HIV Testing Rate



Note: This figure shows triple-differences event study coefficients for the HIV testing rate using data from the BRFSS. The introduction of PrEP is indicated by the vertical dashed red line. The exact regression specification is described in Appendix A.3.

Figure A3.14: Fraction of Male Respondents Reporting Never Using Condoms, by Sexual Orientation



Note: This figure shows the fraction of heterosexual men (blue squares) and MSM (black circles) who report never using condoms during sex in the NHANES. The introduction of PrEP is indicated by the vertical dashed red line.