Unintended Consequences of Life-Saving Pharmaceutical Innovations: How HAART Led to the Resurgence of Syphilis*

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Abstract

Syphilis, a sexually transmitted infection that can lead to serious health complications, was almost eliminated in the United States by 2000. But since then, its incidence began to increase, recently reaching a 60-year peak. We suggest that the introduction of the Highly Active Antiretroviral Therapy (HAART) drug regimen, which transformed HIV into a manageable chronic disease, is partly responsible, as HIV+ and HIV- individuals altered their sexual behavior after the introduction of HAART. To test this empirically, we exploit plausibly exogenous variation in HAART takeup based on pre-HAART AIDS prevalence, sex, and time in a triple differences framework. We find that a one standard deviation increase in the pre-HAART AIDS prevalence rate led to a 21% increase in the syphilis incidence rate, and that in the absence of HAART, there would have been 78% fewer syphilis cases. We also provide estimates for the cases attributable to averted HIV deaths. These results highlight the need to consider unintended consequences that could stem from behavioral changes following the introduction of life-saving medical innovations.

Keywords: HAART, HIV, LGBTQ+, Moral Hazard, Unintended Consequences

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1 Introduction

During the latter half of the 20th century, the incidence rate of syphilis fell by over 97 percent, from a peak of 447 cases per 100,000 in 1943 to an all-time low of 11.2 per 100,000 in 2000.[1,2] The initial decline has been attributed in large part to the expanded use of Penicillin, while changes in sexual norms helped to continue this trend (CDC, 2024b; Fenton and Imrie, 2005). This sustained decline lent hope to the prospect of eliminating syphilis altogether (Shockman et al., 2014), as evident in the Centers for Disease Control and Prevention's (CDC) 2000 "Syphilis Elimination Communication Plan" which called for the elimination of syphilis by 2005 (CDC, 2020).

During this time of declining syphilis incidence, HIV emerged as a major cause of death in the US beginning in the 1980's. By 1993, it was the most common cause of death among individuals aged 25-44, and was particularly prevalent among men who have sex with men (MSM) (CDC, 1996).[3] Although several drugs were developed to treat HIV infection as early as 1987, these drugs were only effective for a limited duration and had severe side effects. In 1996, researchers had a major breakthrough when they found that a three-drug regimen comprised of recently developed drugs, referred to as HAART (highly active antiretroviral therapy), could effectively suppress the replication of the virus over long periods. Despite taxing side effects, HAART transformed HIV infection from a mostly fatal condition to a chronic manageable one (NIAID, 2018). As the use of HAART grew, annual HIV deaths started to decline rapidly from a peak of approximately 42,000 in 1995 to under 14,500 by 2000.[4]

Shortly after the introduction of HAART and the subsequent reduction in HIV deaths, the long-running trend of declining syphilis incidence began to reverse (see Figure 1). However, this reversal was only observed among men, the primary users of HAART. In 2001, the syphilis incidence rate exceeded that of the previous year's for the first time since 1943. Syphilis incidence continued to rise rapidly, reaching a 60-year peak of 62.2 per 100,000 in 2022 (203,500 new cases), a 7.6-fold increase since the year 2000 (CDC, 2024b). This increase has been dubbed "out-of-control" by the National Coalition of STD Directors (NCSD) and "crisis level" by the Department of Health and Human Services (HSS) (NCSD, 2024; Levine, 2024). As a

[1] Syphilis is a bacterial infection that is spread primarily through sexual contact. If left untreated, it can lead to serious health complications. These figures include all stages of syphilis and congenital syphilis.

[2] Prevalence refers to all existing cases, while incidence refers to *new* cases.

[3] In 1993, 56.0% and 47.1% of male and total AIDS cases, respectively, were attributed to MSM (CDC, 1995a). In 2023, 83.3% and 67.3% of male and total HIV cases, respectively, were attributable to MSM (CDC, 2024a).

[4] Authors' calculation using CDC WONDER underlying cause of death database (of Health et al., 2019).

consequence, HSS recently set up a multi-agency National Syphilis and Congenital Syphilis Syndemic Task Force to lead the public health response.

In this paper, we argue that the resurgence of syphilis at the turn of the 21st century was in large part a direct result of the introduction of HAART. There are two key mechanisms which could drive this result. First, the introduction of HAART may have led to changes in the sexual behavior of both HIV-positive and HIV-negative individuals. Among the former, both an improvement in health and the reduced likelihood of infecting potential partners with HIV likely led to an increase in risky sexual behavior, while among the latter, a reduced risk of contracting HIV and the reduced cost of living with HIV likely led to an increase in risky sexual behavior as well. Second, the introduction of HAART saved the lives of thousands of individuals with HIV, allowing them to lead relatively normal lives. A natural consequence of this increased longevity is an increase is the contraction of sexually transmitted infections (STIs) among those lives saved, even absent any changes in sexual behavior. We present evidence that both mechanisms play a role in the rise of syphilis rates, although increased longevity alone cannot explain our results.

In order to empirically evaluate the effect of the introduction of HAART on syphilis incidence, we estimate a triple differences event study model leveraging variation in exposure to HAART along two margins: pre-HAART AIDS prevalence and sex. The rationale behind the first difference, pre-HAART AIDS prevalence, is that states with a higher prevalence of AIDS prior to the advent of HAART were much more likely to be affected by its introduction. The second difference, sex, relies on the facts that syphilis trends were nearly identical for males and females prior to the introduction of HAART (see Figure 1), but due to their higher HIV/AIDS prevalence, males had significantly higher takeup of HAART. This allows us to use sex to net out any time-varying factors that could have affected syphilis incidence rates in a given state-year (e.g., local public health campaigns), provided these factors did not vary by sex.

We first verify, using a difference-in-differences event study estimator, that states with higher pre-HAART AIDS prevalence were indeed the states that had the highest takeup of HAART.[5] We then show, using the same difference-in-differences model, that these same states saw immediate reductions in both male and female HIV death rates. However, the decline was much more pronounced among males, consistent with their higher baseline AIDS prevalence and takeup of HAART. Both the male and female event study coefficients exhibit some pre-trends, although these pre-trends are almost identical across sex. This motivates our triple differences model, in

[5] We do not have data on HAART prescriptions by sex, which is why we do not estimate a triple differences regression for this outcome. But, other literature shows that HAART was taken up primarily by males, as detailed in Section 4.

which the pre-trends are netted out by the inclusion of sex as an additional difference.

We then present our main finding: following the introduction of HAART, syphilis incidence began increasing differentially among males in states which previously had higher AIDS prevalence. As noted in the prior paragraph, these are precisely the states where HAART prescriptions were most widespread and where HIV deaths fell the most. These effects occur with a delay, which is consistent with the typical progression of syphilis symptoms, typical delays in diagnosis, and slow changes in sexual norms following a change in HIV risk. Overall, our results suggest that the introduction of HAART led to approximately 53,500 additional syphilis diagnoses between 1996 and 2006, relative to what we would have expected in the absence of HAART. In a back-of-the envelope, we show that these results cannot be entirely explained by increased longevity among HIV+ individuals, suggesting some degree of moral hazard.

Our findings have important policy implications. Foremost, they highlight the need for public health practitioners to consider individuals' potential behavioral responses to medical innovations that alter their incentives: in our case, potential changes in sexual behavior that followed the introduction of HAART. Individuals who increased their risky sexual behavior in response to the decrease in its "price" might have been better off even at the private cost of increased likelihood of contracting STIs. But, it is possible that these individuals hold inaccurate information on these private costs (e.g. they are unaware of the potential severity of syphilis) and are not internalizing the social costs of the additional STIs, such as the added risk to others and the increase in the risk of antibiotic resistance. To the extent that the costs of increased STI prevalence are not fully internalized, public health practitioners may wish to consider additional measures to combat the spread of STIs resulting from behavioral responses to better STI treatments. Such measures could include more frequent testing for syphilis, which is not tested as often as other STIs (Chow et al., 2017; Gray et al., 2010), expanding local public health services, and increased use of post-exposure prophylaxis (PEP)(CDC, 2024c).

2 Background and Related Literature

2.1 Syphilis Background

Costs associated with HIV are well known (Hutchinson et al., 2006). However, STIs other than HIV are also costly, and more prevalent. In 2018, more than 2.5 million new cases of chlamydia, gonorrhea, and syphilis, the three most commonly tracked STIs, were reported in the United States.

When including STIs that are not commonly tracked, such as Human papillomavirus (HPV), the estimated number of new cases rises to 26 million (CDC, 2022). These resulted in $2.2 Billion dollars in direct medical costs (Chesson et al., 2021), in addition to numerous indirect costs such as decrease in work and productivity, pain, infertility, and decrease in quality of life.

Syphilis is estimated as the third costliest STI per infection, after HIV and Hepatitis B (Chesson et al., 2021).[6] Syphilis is a bacterial infection whose progression in adults is categorized into four stages - primary, secondary, latent, and tertiary. The first two stages occur within a few months of infection and are characterized by symptoms that resolve with or without treatment as the infection progresses into its latent stage, which could last for years. Left untreated, the infection eventually progresses into its tertiary stage, in which the infection affects multiple organ systems and could be fatal. Syphilis is usually treated with Penicillin, which prevents disease progression but does not undue any damage that the disease has caused. Thus, even if treated, an infection diagnosed in its later stages could lead to serious permanent health complications. Syphilis can also spread from an infected pregnant woman to her unborn baby, leading to congenital syphilis, a severe, life threatening condition (CDC, 2023b).

In recent decades, MSM have been disproportionately affected by syphilis. Heffelfinger et al. (2007) estimate that in 2003, 62% of all syphilis cases were among MSM; other authors provide similar estimates (Douglas Jr et al., 2005; de Voux, 2017).[7]

2.2 Related Literature

The effect of HAART on risky sexual behavior has been examined in the economics and public health literature with mixed findings. Using a sample of ≈1,400 HIV-positive men surveyed between 1996 and 1998, and exploiting variation in Medicaid eligibility, Lakdawalla et al. (2006) estimate that HAART more than doubled the number of sexual partners of HIV-positive individuals. Similarly, using a sample of ≈2,500 MSM surveyed in four sites, Chan et al. (2016) find that both HIV-positive and HIV-negative individuals were more likely to engage in high-risk

[6] Syphilis infection is costlier than chlamydia and gonorrhea infections due, among other reasons, to more severe potential complications, higher probability of leading to HIV, and the extremely high cost of congenital syphilis (Chesson et al., 2008).

[7] Unlike with HIV, national surveillance data on other STIs do not detail incidence by MSM status. Thus, the share of STI incidence by MSM status detailed in the following studies are deduced from the change in the male-female incidence ratio, as well as from local studies for which MSM status is available.

sex after the introduction of HAART.[8] In contrast, a highly cited meta-analysis of public health papers on the topic concluded that HIV-positive individuals who were using HAART did not exhibit increased risky sexual behavior (Crepaz et al., 2004), while a more recent meta-analysis even suggests that some risky sexual behavior decreased among HIV-positive individuals who were using HAART, possibly explained by self-selection and exposure to prevention messages during treatment (Doyle et al., 2014).

Our paper contributes to this literature in several ways. First, our outcome of interest is syphilis diagnoses rather than sexual behavior. While the latter outcome is an important mechanism in determining STI rates, the association is not necessarily straight-forward.[9] Furthermore, our data encompasses the universe of STI diagnoses across the United States, in contrast to the small, usually local and self-selected samples used in previous studies.[10] Specifically, we focus on the causes for the resurgence of an STI that is one of the costliest (see Section 2.1), and that has been on the public agenda in recent years. Second, we employ rigorous causal inference methods in contrast to most previous studies.[11] Third, although not our main focus, we are the first to causally estimate the effect of the introduction of HAART on HIV/AIDS deaths.[12] Lastly, we add to the growing economics literature that explores the unintended consequences of medical innovations (e.g., Eilam and Delhommer, 2022; Beheshti, 2019; Doleac and Mukherjee, 2022).

3 Data

We obtained data on STIs other than HIV by special request from the CDC, which provided incidence data for syphilis and gonorrhea at the state $\times$ year $\times$ sex $\times$ race level, as well as the corresponding population estimates, for each of the 50 states and the District of Columbia

[8] The paper's main goal is to develop a framework to evaluate medical innovation rather than causally estimate the effect of HAART on risky sexual behavior.

[9] For example, increases in the average number of sexual partners might not translate into an increase in STIs if there is an increase in the use of protection.

[10] See Scheer et al. (2001), for example.

[11] For example, in their literature review Crepaz et al. (2004) note that the vast majority of studies examining the association between HAART and risky sexual behavior are comparisons between HIV-positive individuals who are or are not taking HAART. Lakdawalla et al. (2006) is an exception.

[12] We are not claiming to be the first to estimate the impact of HAART itself on HIV/AIDS deaths, which has been widely studied. Rather, we estimate the reduced form impact of HAARTs introduction in the US.

between 1992 and 2006 (CDC, 2008).[13,14] We construct a panel dataset from 1992, 4 years before the introduction of HAART, to 2006, 10 years after the introduction of HAART. Using these data, we calculate our main outcome variables: the incidence rates of syphilis and gonorrhea per 100,000 for ages 15-44 at the state $\times$ year $\times$ sex level , in aggregate and by race.

We obtained data on HIV from the CDC's HIV/AIDS Surveillance Report (CDC, 1995b), from which we constructed our main treatment variable - the AIDS prevalence rate per 100,000 by state in 1995, the year before the introduction of HAART.[15,16]

We obtained several additional variables for our "first stage" analysis. First, we obtained data on the HIV/AIDS death rate per 100,000 at the state $\times$ year $\times$ sex level from 1992 to 2006 from the CDC Wonder database (CDC, National Center for Health Statistics. National Vital Statistics, 2023). Second, we acquired data on HAART prescriptions from IMS Health (now IQVIA), an international consulting and data services firm that supplies the pharmaceutical industry with sales data (IMS Health, 2008). The data covers 90% of all pharmaceutical sales in the United States. It includes the number of prescriptions separately for each HIV drug at the county $\times$ month level from 1996 to 2004. We categorize as "HAART" drugs those of the protease inhibitors and the non-nucleoside reverse transcriptase inhibitor drug classes, which were introduced in 1996 or after, and were main components of the HAART regimen (HIVinfo, 2024; Levy, 2024), and aggregate these to the state $\times$ year level.[17] Then, combining this with the population data, we calculate the rate of HAART prescriptions per 100,000.

4 Research Design

Our goal is to estimate how the introduction of HAART affected the spread of syphilis. To that end, we estimate a continuous triple-differences style model comparing males versus females in states that were more likely to be affected by the introduction of HAART to states that were less likely to be affected, before and after HAART became available. Our proxy for the extent to which different states were likely to be affected by the the introduction of HAART is the AIDS prevalence

[13] Chlamydia data is only reliably available from 1996 so is omitted from our analysis.

[14] The database includes incidence data of primary and secondary syphilis, which are diagnosed close to the time of infection. It does not include incidence data of later stages of syphilis, which are rarer, and are potentially diagnosed years after infection, nor does it include incidence data of congenital syphilis, which is less relevant in our context.

[15] This measure includes all ages, sexes, and races.

[16] Standardized HIV prevalence (as opposed to AIDS prevalence) data was not readily available for all states in 1995.

[17] These include Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir/ritonavir, Atazanavir, Fosamprenavir, Nevirapine, Delavirdine, Efavirenz, and Emtricitabine.

in each state in 1995, the year before the introduction of HAART.[18] We show a map of this variable in Figure 3.

The comparison between males and females essentially uses females as a control for factors that can vary across both time and state, provided they affect both sexes equally. This is potentially important if there are any state-specific policies that vary over time targeting reductions in STIs. Females had substantially lower rates of HIV/AIDS prior to the introduction of HAART (Figure 1, Panel (a)), and were therefore less likely to be affected by its introduction–regardless of the AIDS prevalence in the state.[19] Indeed, Gebo et al. (2005); King et al. (2008) find substantially lower HAART takeup for HIV+ females relative to HIV+ males. This, in addition to their lower baseline rates of HIV/AIDS supports their inclusion as an additional control group.

4.1 Difference-in-Differences

We do not have data on HAART prescriptions by sex. So for our first stage, we consider continuous event study difference-in-difference regressions (Callaway et al., 2024). We also show present results from this model for sex-specific HIV deaths in order to illustrate the idea behind our main triple differences specification. Specifically, we consider regressions of the form:

$$y_{st} = \alpha_s + \gamma_t + \sum_{T \neq 1995} \beta_T \cdot 1(year = T) \cdot AIDS_s^{pre} + \delta X_{st} + \epsilon_{st} \tag{1}$$

Where y_{st} is the outcome either the HAART take-up rate or the HIV death rate in state s and year t. We include state fixed effects (α_s) to control for time-invariant differences between states that could affect STIs that could potentially affect our outcomes, and year fixed effects (γ_t) in order to account for any common trends across the country. The X_{st} term is a vector of controls which varies at the state-year level.[20] Our treatment variable, $AIDS_s^{pre}$, is the prevalence rate of AIDS in 1995 in state s. Under the strong parallel trends assumption, which we discuss in the following paragraph, the β_T coefficients measure variance-weighted movements along the dosage response function between states with different baseline AIDS prevalence rates relative to 1995, the omitted year (Callaway et al., 2024). Standard errors are clustered at the state level throughout.

[18] In results not shown here, we replicate our analysis with two alternate measures: (1) the pooled HIV incidence rate in each state from 1990-1994, and (2) the share of MSM in each state prior to the introduction of HAART (Shahid, 2023; Eilam and Delhommer, 2022). The idea with the latter variable is that, since MSM accounted for a disproportionate share of HIV/AIDS cases prior to the introduction of HAART, states with higher shares of MSM were more likely to be affected by its introduction. All three variables yield very similar results.

[19] To the extent that there are effects for females, we'd expect these to attenuate our estimates.

[20] In our baseline model, we omit any control variables. In results not presented here, we find no meaningful differences when controlling for the racial and age composition of the population or various economic indicators.

We make two identifying assumptions, which together form the *strong parallel trends* (SPT) assumption. The first is that trends in the outcome would have been similar in states with higher and lower pre-HAART AIDS prevalence if not for the introduction of HAART. This is an assumption about a state of the world that was not realized, and is therefore not directly testable. However, we plot the β_T coefficients in each year prior to the introduction of HAART in order to assess its plausibility. The second is that the average treatment effect on the treated (ATT) is equal for all units with identical dosages. In practice, this latter assumption means that there is no sorting into dosages across states based on anticipated returns to HAART. This assumption is quite plausible—it is highly unlikely that, prior to the introduction of HAART, individuals migrated to states with different 1995 AIDS prevalence because they expected HAART to have differential effects in these states.

In section 5, we find that there are strong dynamics in our effects over time, underscoring the appropriateness of our event study approach. However, in order to summarize our effects we also present estimates from a more traditional difference-in-differences model of the form:

$$\begin{aligned} y_{st} = \alpha_s + \gamma_t + \beta_{transition} \cdot 1(1996 \leq t \leq 2000) \cdot AIDS_s^{pre} \\ + \beta_{post} \cdot 1(t > 2000) \cdot AIDS_s^{pre} + \delta X_{st} + \mu_{st} \end{aligned} \tag{2}$$

Where all terms are defined as above. This specification splits our sample into three ranges of time: the pre-HAART period (1992-1995), a transition period in which HAART takeup rose and then stabilized (1996-2000), and a period after HAART had been widely adopted (2001-2006). We use the estimate of β_{post} as a summary of the long-term effect of the introduction of HAART.

4.2 Triple Differences

For our main outcome, we present evidence from a triple differences specification. The estimating equation is:

$$
\begin{aligned}
y_{stg} = \mu_{sg} + \phi_{gt} + \delta X_{st} \\
&+ \sum_{T \neq 1995} \alpha_T \cdot 1(year = T) \cdot AIDS_s^{pre} \\
&+ \sum_{T \neq 1995} \beta_T \cdot 1(year = T) \cdot AIDS_s^{pre} \cdot 1(g = male) \\
&+ \xi_{stg}
\end{aligned} \tag{3}
$$

where μ_{sg} are state-by-sex fixed effects, ϕ_{gt} are sex-by-year fixed effects, and the β_T coefficients are the triple-differences coefficients representing movements along the dosage response function for the difference in male and female outcomes between places with higher and lower values of $AIDS_s^{pre}$ in each year relative to 1995. Similar to equation 1, we invoke the strong parallel trends (SPT) assumption. This assumes that, in the absence of HAART, trends in the male-female outcome gap would have evolved similarly over time across states with differing 1995 AIDS prevalence rates (Olden and Møen, 2022). Furthermore, SPT assumes equal ATTs for all units with identical dosages (Callaway et al., 2024).

We also present coefficients from a triple differences specification analogous to equation 2 as a summary measure of the long-run effect of the introduction of HAART. The inclusion of a transition period allows for changes in syphilis to occur with a delay. This is likely as syphilis is not regularly tested, and its symptoms are often misdiagnosed causing further delays in detection. Furthermore, we expect any moral hazard effects to take time to manifest, as it likely takes time for sexual norms to evolve.

5 Results

5.1 First Stage

We display the national rate of HAART prescriptions over time in panel (a) of Figure 2. This figure shows the immediate rise in HAART prescriptions beginning with its introduction in 1996. Prescriptions continued to grow for several more years, but began to flatten out with the introduction of modern antiretrovirals in 2001.[21]

We first show evidence that states with higher AIDS prevalence rates before the introduction

[21] Modern formulations, dubbed "ART", proved to have far fewer side effects relative to earlier HAART formulations.

of HAART were in fact the states most affected by its introduction. We do so in panel (c) of Figure 2, where we plot the β_T coefficients from equation 1 with the number of HAART prescriptions per 100,000 population as the outcome variable. Since HAART did not exist prior to 1996, the coefficients are mechanically equal to zero in the pre-period. However, the coefficients become positive in 1996 and continue to grow in magnitude until about 1999, after which they stabilize. We note that these coefficients represent the *difference* in the HAART prescription rates in states with one more pre-HAART AIDS case per 100,000, relative to 1995. For example, the $\hat{\beta}_{2000}$ coefficient of approximately 54.4 indicates that an additional pre-HAART AIDS case was associated with approximately 54.4 additional HAART users in the year 2000 relative to 1995. We do not have data on HAART prescriptions by sex at the state level, but other research suggests that the vast majority of HAART users during this time period were males (Gebo et al., 2005; King et al., 2008).

We present the summary results from equation 2 in Panel (a) of Table 1. Specifically, column (1) reports the coefficients on the interactions of the indicators for the transition period (1996-2000) and post period (2001-2004) with the 1995 AIDS prevalence rate. Scaling the coefficient of interest, 52.24, by a one standard deviation in the treatment variable (84.08), indicates that a one standard deviation increase in pre-HAART AIDS exposure was associated with and additional 4,561 annual HAART prescriptions per 100,000.

In panels (b) and (d) of Figure 2, we examine how this translated into reductions in HIV deaths. We first show the raw time series for the HIV death rate by sex in panel (b). This figure shows both the dramatically higher HIV prevalence for males relative to females, as well as the sharp drop in HIV deaths following the introduction of HAART. Turning to our regression specification, we again estimate equation 1, this time with the HIV death rate as the outcome variable. We estimate this equation separately by sex, with the coefficients for males shown as blue circles and for females as gray squares. In each post-period, the coefficients for males are substantially larger in magnitude than the coefficients for females. This is consistent with the fact that males and MSM in particular were the primary group that was suffering from HIV/AIDS deaths prior to the introduction of HAART, and therefore the group that stood to gain the most from its introduction .

The corresponding results from equation 2 for these outcomes, as well as aggregate HIV Deaths, are shown in columns (2) through (4) of Panel (a) of Table 1. Pooling males and females together in column (2), we find that a one standard deviation increase in pre-HAART AIDS prevalence is associated with 12.11 (84.08×0.144) fewer HIV deaths per 100,000, a 81.04 percent decrease relative

to the pre-period mean. Breaking this down by sex, a one standard deviation increase in pre-HAART AIDS exposure is associated with 21.10 (84.08×0.251) and 3.86 (84.08×0.0459) fewer HIV deaths per 100,000 for males and females, respectively.

Overall, these results show that HAART had larger benefits for males relative to females, especially in states with a high concentration of AIDS. This difference by sex underscores the rationale for our triple-differences regression strategy in the following subsection. The fact that HAART also led to reductions in HIV deaths for females suggests that our results will be a lower bound on the effect of the introduction of HAART on STIs.

5.2 Main Results

Syphilis In this subsection, we present our main triple differences results. Specifically, we estimate equation 3 with the syphilis incidence rate as the dependent variable and present the results in panel (a) of Figure 4. Prior to the release of HAART in 1996, the coefficients generally hover around zeros and do not show any obvious pattern. The coefficients remain close to zero during most of the transition period, until they become positive and statistically significant in each year after 1999. This delayed pattern is consistent with the dynamics of HAART take-up, as well as typical delays in detection and diagnosis (CDC, 2023b).[22] Likewise, we expect any moral hazard effects to take time to manifest. By the end of our sample period in 2006, the coefficient is 0.065, indicating that an additional pre-period AIDS case is associated with 0.065 additional male syphilis diagnoses (per 100,000) relative to female diagnoses compared to 1995. The summary coefficient for the post period shown in column (1) of Panel (b) of Table 1 is 0.0446. Scaling this by a one standard deviation change in the pre-period AIDS prevalence rate, this implies an increase of 3.75 (84.08×0.0446) annual cases of syphilis per 100,000, or an approximately 21.00 percent increase relative to the pre-period mean.

During this time period, there were significant differences in baseline STI rates by race. For example, while the average syphilis incidence rate in the pre-period (1992-1995) was equal to 17.56 per 100,000, the rate among whites was 2.06 compared to 121.69 among blacks. Motivated by these differences in levels, we examine potential heterogeneity by race in panels (b) through (d) of Figure 4. Panel (b) shows the triple differences coefficients from a regression in which we

[22] Lower syphilis incidence rates compared to gonorrhea and chlamydia, as well as a diagnosis that usually requires a blood test rather than a swab, result in lower rates of syphilis testing compared to gonorrhea and chlamydia (Davis and Gaynor, 2020; White et al., 2012). Moreover, as mentioned in Section 3, beside the fact that primary and secondary syphilis symptoms usually go away even without treatment, they can be overlooked, and even if not overlooked, can be mistaken for other conditions.

only consider whites, while panel (c) shows the results for blacks and panel (d) shows the results for Hispanics. The qualitative pattern for all groups is quite similar, with a larger coefficient for black and Hispanics compared to whites. However, in percentage terms, the increase for whites is substantially larger due to the much lower baseline. A one standard deviation increase in pre-HAART AIDS prevalence corresponds to a 185.30 ($\frac{84.08\times.0454}{2.06}$) percent increase above the mean for whites and a dramatically smaller 5.00 ($\frac{84.08\times.0724}{121.69}$) percent increase above the mean for blacks.

Gonorrhea We present the event study results for gonorrhea in Figure A1. As in the previous figure, panel (a) shows the results for the aggregate while panels (b) and (c) show the results broken down by race. The coefficients in panel (a) are consistently near zero, indicating no changes in overall gonorrhea cases attributable to the introduction of HAART. We find little evidence of heterogeneity by race. The summary coefficients are included in columns (5)-(8) of Panel (b) of Table 1. Consistent with the event studies, columns (5) through (8) show coefficients that are statistically insignificant.

The lack of statistically significant and economically meaningful results for gonorrhea are consistent with the fact that introduction of HAART primarily affected MSM. Whereas a large proportion of syphilis cases were among MSM (see Section 3) , only a small fraction of gonorrhea cases were among MSM. For example, Fox et al. (2001) find that in 1999, only 13.2% of gonorrhea cases in 29 STI clinics were attributable to MSM, which is likely an overestimate since MSM are more likely to visit STI clinic than non-MSM. Rietmeijer et al. (2003) finds a similar result (12.9%) for 1996-2001 from a Denver health clinic.

5.3 Counterfactuals

In order to summarize the magnitude of our syphilis effects, we conduct a simple simulation in which we predict the growth of syphilis under the counterfactual where cumulative pre-period AIDS cases were equal to zero. The idea behind this simulation is that, if AIDS did not exist, then there would be no take-up of HAART and therefore no expected effects of its introduction. Specifically, we estimate the parameters from equations 1 and 3, then compute the predicted outcomes under the observed value of $AIDS_s^{pre}$ and when setting $AIDS_s^{pre} = 0$. We then aggregate the difference between these values from 1996 to 2006 to provide our estimate of the cumulative effect of HAART.

Our results indicate that, in the absence of HAART, we would have observed about 53,562 fewer cases of syphilis in the two decades after HAARTs release. In percentage terms, this is a reduction of 78 percent compared to what we actually observed during this period. A natural question, however, is the extent to which this disparity is driven by behavioral changes (e.g., increases in risky sexual behavior) or the result of typical levels of new STIs among those whose lives were saved by HAART. We turn our attention to these question in the following subsection.

5.4 Mechanisms

We now discuss the two most likely drivers behind the observed increases in syphilis following the introduction of HAART: (1) increases in risky sexual behavior, which we term moral hazard, and (2) increases in syphilis among those whose would have otherwise died of HIV/AIDS. We note that these are not mutually exclusive explanations, as there were likely moral hazard effects among those whose lives were saved by HAART.

Moral Hazard By significantly reducing the viral load of HIV-positive individuals, HAART transformed HIV/AIDS from a terminal condition into a manageable chronic disease and considerably reduced their risk of infecting others (CDC, 2023a). These two factors led to a decrease in the "price" of sex for both for HIV-negative and HIV-positive individuals. For those without HIV, the likelihood of contracting it declined due to reduced viral loads among the HIV-positive, and if contracted, the availability of effective treatment meant that its consequences were dramatically reduced. For HIV-positive individuals, the price declined as they were now less likely to infect others.[23] This decrease in price could have led to an increase in the prevalence of risky sex, which in turn would increase the incidence of STIs. This is especially likely for STIs like syphilis, which were concentrated among MSM. Several studies support this hypothesis; as mentioned in Section 1, Lakdawalla et al. (2006) find that HAART led to more than doubling in their number of sexual partners of HIV-positive individuals and Chan et al. (2016) find that both HIV-positive and HIV-negative individuals were more likely to engage in high-risk sex after the introduction of HAART.

STIs Among Averted HIV Deaths Another possible explanation for the increase in syphilis is that–in a world without HAART–many individuals would have died of HIV/AIDS. Instead, these

[23] Sex with condoms is not fully protective against contracting HIV if exposed to the virus (Pinkerton and Abramson, 1997).

individuals go on to lead relatively normal lives, and many go on to contract other STIs such as syphilis. This would lead to very different welfare and policy implications from a world in which the observed increase in syphilis was due entirely to moral hazard.[24] While it is certainly the case that some of the rise in syphilis was attributable to HIV+ individuals who would have died without access to HAART, it is not immediately obvious how much of the total increase in syphilis this explains. This is further complicated by the fact that data on syphilis incidence by sex and sexual orientation during our study period is scarce. In order to investigate the extent to which our results can be driven by this channel, we conduct a series of back-of-the-envelope calculations under differing assumptions about the incidence of syphilis.

As discussed in section 5.3, we estimate that the introduction of HAART led to 53,562 new cases of syphilis between 1996 and 2006. Using the same triple differences methodology, we also estimate a reduction in HIV/AIDS deaths of 193,074 over the same period.[25] This suggests that every 3.6 averted HIV/AIDS death led to approximately one additional case of syphilis during our 11-year study period. In order to examine whether this is plausibly the result of normal syphilis patterns among the averted deaths, we estimate the number of expected syphilis cases among the lives saved by HAART using various syphilis incidence rates from the literature.

For example, Peterman et al. (2015) estimate that, at the peak pre-HAART spread of syphilis in 1982, the annual incidence of syphilis among MSM in the US was 340 per 100,000. If we apply this rate to our triple differences estimate of HIV deaths averted over our sample period (assuming all lives saved were MSM), this would result in 3,567 additional cases of syphilis.[26] In contrast, a meta-analysis by Zheng et al. (2024) estimates a syphilis incidence rate among MSM in the US of 4,280 per 100,000, over 10 times greater than Peterman et al. (2015). At this rate, we would predict 44,903 cases of syphilis. The reason for these discrepancies is that the latter estimates come from more recent literature when the incidence of syphilis among MSM has risen significantly. This latter syphilis rate is significantly higher than the rate in the mid-19990s and early 2000s, and thus provides an upper bound on the number of syphilis cases that can be accounted for by averted HIV deaths. Ideally, we would use estimates of the incidence of syphilis among MSM in each year,

[24] For example, a world in which everyone died of a novel disease would be a world without STIs, although it would be odd to count the decrease in STIs as a benefit in some sort of cost-benefit analysis.

[25] This is an underestimate of the total number of lives saved by HAART, as it measures the gap in the number of male and female lives saved. Using a simple difference-in-differences pooling males and females, we estimate 318,685 total lives saved. However, for the purposes of this calculation we use the former number, as it corresponds to our estimates of the effect of HAART of syphilis.

[26] We arrive at this figure by multiplying the total number of life-years saved by the annual incidence rate. For example, a life saved in 1996 adds 11 life years to our total, while a life saved in 2006 only adds 1 year.

although this data is not available.

Of course, it is possible that incidence of syphilis among HIV+ MSM could be greater than the rate among MSM as a whole. While we were unable to locate estimates of the annual incidence of syphilis among HIV+ MSM during this period, Zheng et al. (2024) provide recent prevalence estimates. Specifically, they estimate syphilis prevalence among MSM and HIV+ MSM at 7.74 and 17.5 percent, respectively. Multiplying these number by the total number of deaths averted yield estimates of 14,944 and 33,788 syphilis cases, respectively.

Taken together, these calculations provide a wide range of plausible values for the fraction of the syphilis increase that could be accounted for by averting HIV deaths, from approximately 6.7 percent on the low end to approximately 83.8 percent on the high end.

6 Conclusion

The discovery of HAART was one of the greatest medical breakthroughs of the last 30 years. Hundreds of thousands of individuals who would have otherwise died have instead been able to lead healthy, productive lives.

In this paper, we show that the introduction of HAART is partially responsible for the resurgence of syphilis in the US. This is likely the result of both moral hazard and increased longevity among a particularly high-risk group (HIV-positive MSM). While the benefits of HAART (decreased mortality from HIV) far exceed the costs (increases in the spread of syphilis), these latter consequences are still important to document. We argue that these consequences are a predictable result of individuals responding to changes in the perceived risk of contracting HIV, and the cost of HIV if contracted. While these changes may be individually rational, they likely carry significant external costs which are not being accounted for. To the extent that these externalities exist, they may justify public policy responses to address the increasing spread of STIs, such as increases in testing.

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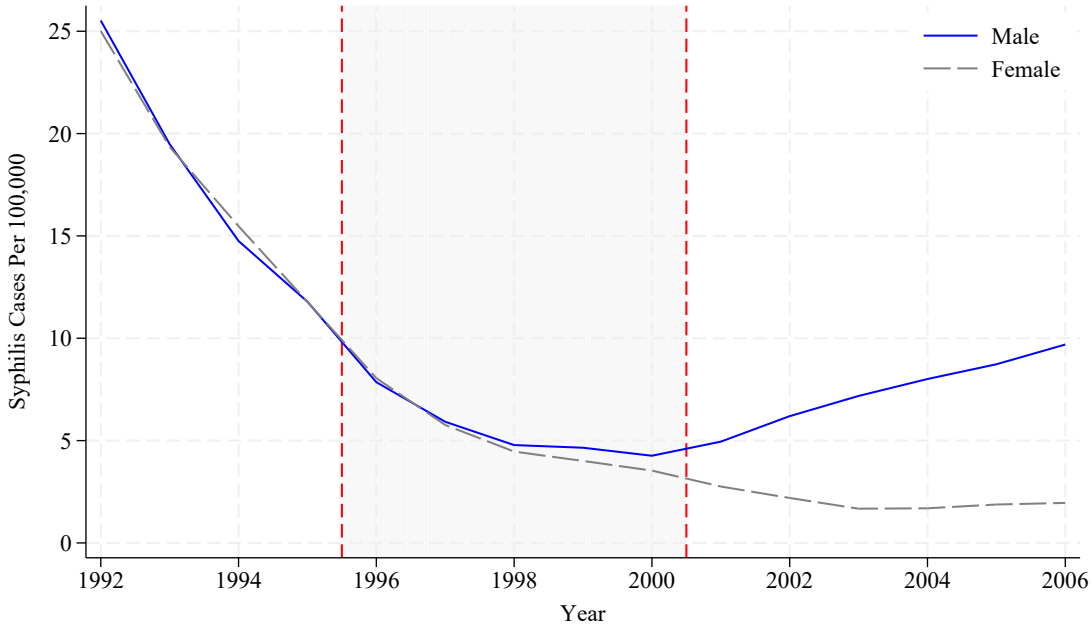
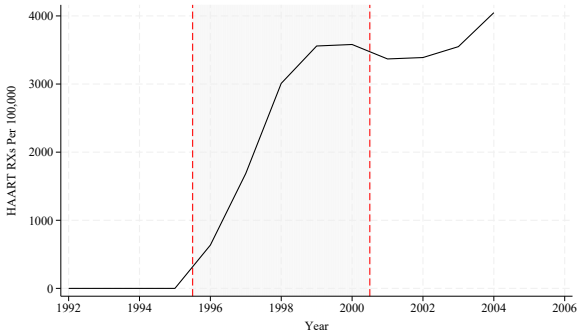
7 Figures and Tables

Figure 1: Syphilis Incidence Rate Over Time by Sex

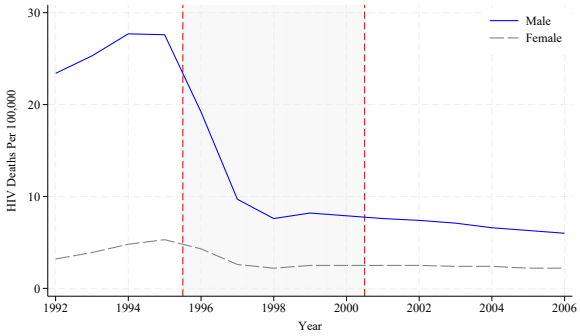


Note: This figure shows the annual rate of syphilis cases per 100,000 among individuals aged 15-44. Diagnoses for males are shown as a solid blue line, while diagnoses for females are shown as a dashed gray line.

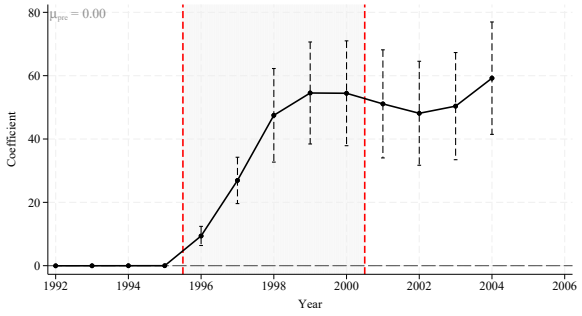
Figure 2: Time Series and Difference-in-Differences Event Studies: HAART Take-Up and HIV Death Rates



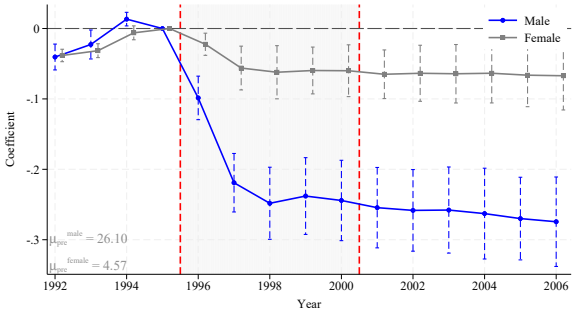
(a) Time Series: HAART



(b) Time Series: HIV by Sex



(c) Regression Coef.: HAART



(d) Regression Coef.: HIV by Sex

Note: The top row shows national level trends in HAART take-up, measured as the number of prescriptions per 100,000 population, in panel (a) and HIV death rates per 100,000 in panel (b). Panel (b) is broken down by sex, with male deaths shown as a solid blue line and female deaths as a dashed gray line. Panels (c) and (d) show corresponding regression coefficients from equation 1. The pre-period means are shown in gray in the bottom figures. The dashed vertical red lines indicate the time that HAART first became available and when it reached stable levels of use, respectively.

Table 1: Main Regression Results

Panel (a): Difference-in-Differences

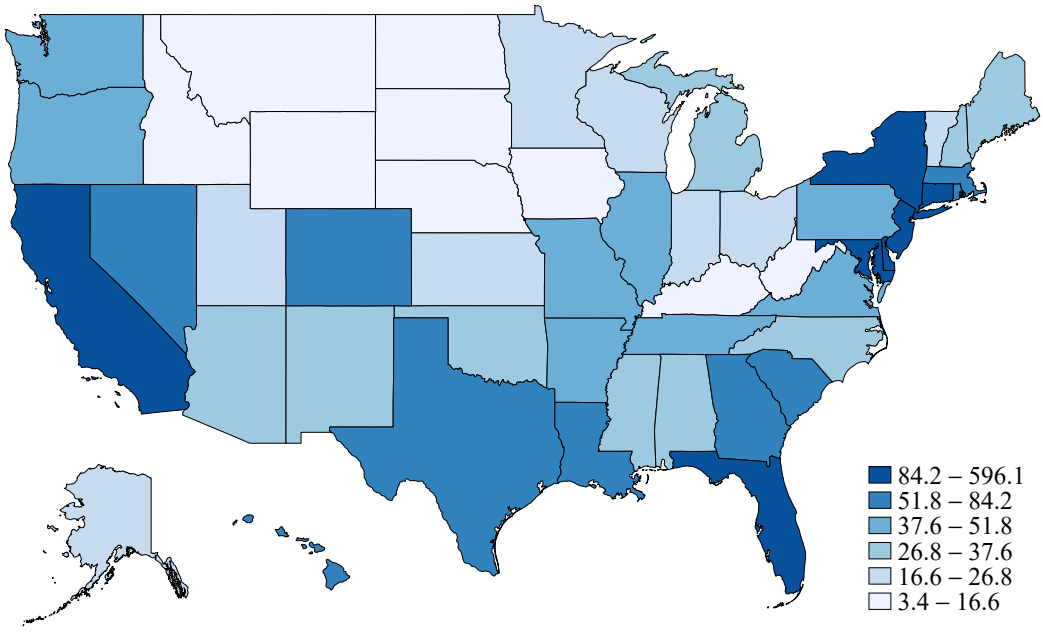
	HAART Rate	HIV Death Rate		
	(1)	(2)	(3)	(4)
	Total	Total	Male	Female
Transition $\cdot AIDS_s^{pre}$	38.79***	-0.112***	-0.197***	-0.0330*
	(5.539)	(0.0176)	(0.0227)	(0.0148)
	(1.155)	(0.00294)	(0.00327)	(0.00434)
Post $\cdot AIDS_s^{pre}$	52.24***	-0.144***	-0.251***	-0.0459*
	(8.353)	(0.0234)	(0.0297)	(0.0203)
N	663	697	682	533
Clusters	51	50	50	42
Pre-Mean	0.00	14.94	26.10	4.57

Panel (b): Triple Differences

	Syphilis				Gonorrhea			
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Total	White	Black	Hispanic	Total	White	Black	Hispanic
Transition $\cdot AIDS_s^{pre} \cdot$ Male	-0.00488	0.000526	0.00370	0.0256	-0.263	-0.0309	0.281	-0.0909
	(0.00516)	(0.00103)	(0.0208)	(0.0130)	(0.293)	(0.0232)	(1.113)	(0.112)
Post $\cdot AIDS_s^{pre} \cdot$ Male	0.0446***	0.0454**	0.0724**	0.0780***	-0.304	0.0578	0.359	-0.0232
	(0.00694)	(0.0157)	(0.0264)	(0.0169)	(0.470)	(0.0477)	(1.833)	(0.108)
N	1530	1530	1530	1530	1528	1528	1528	1528
Clusters	51	51	51	51	51	51	51	51
Pre-Mean	17.86	2.06	121.69	7.49	273.00	49.67	1784.27	111.47

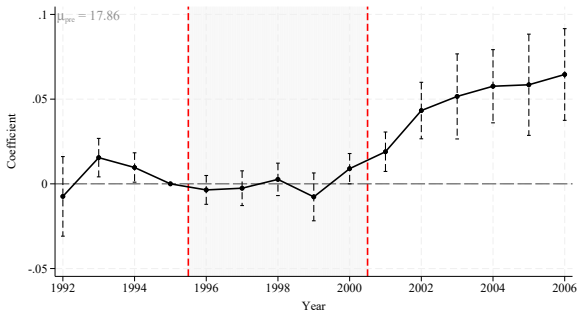
Note: This table shows the regression results from equation 2 and its triple differences analogue in panels (a) and (b), respectively. The dependent variable in column (1) of panel (a) is the HAART take-up rate, while columns (2)-(4) show the results for the HIV death rate in aggregate and by sex. Panel (b) columns (1)-(3) show the triple differences results for syphilis in aggregate and by race. Columns (4)-(6) show the results for gonorrhea.
Standard errors in parentheses. * p<0.05, ** p<0.01, *** p<0.001

Figure 3: Pre-Period AIDS Prevalence Rate

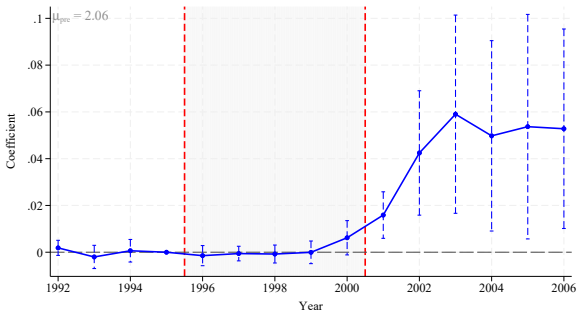


Note: This figure shows a colored map of the US in 1995, with darker shades of blue representing states with a higher prevalence rate of AIDS.

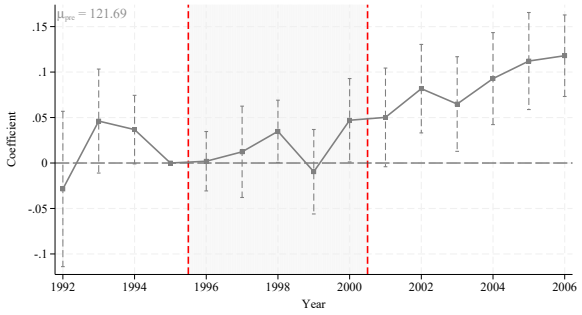
Figure 4: Triple-Difference Event Study: Syphilis Incidence Rate



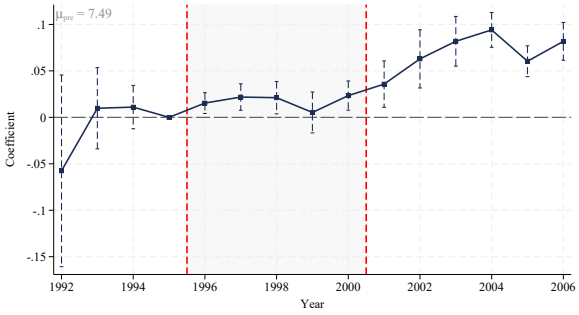
(a) Aggregate



(b) White Only



(c) Black Only

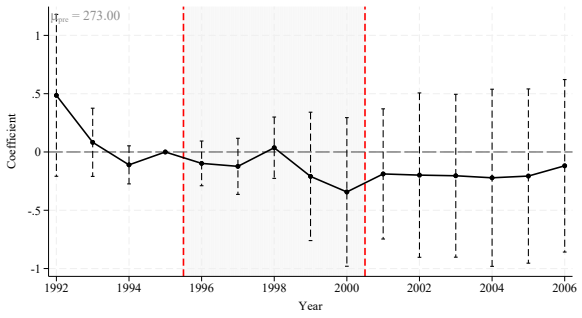


(d) Hispanic Only

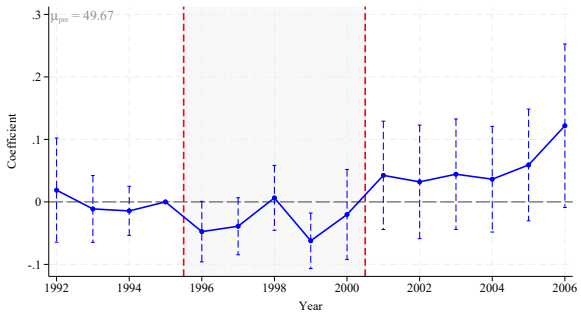
Note: These figures show the triple-differences event study coefficients from equation 3 with the syphilis diagnosis rate as the dependent variable. Panel (a) shows the aggregate results, while panels (b)-(d) show the results for whites, blacks, and Hispanics, respectively. The mean of each dependent variable is shown in the top-left corner of each panel.

A APPENDIX - FOR ONLINE PUBLICATION

Figure A1: Triple-Difference Event Study: Gonorrhea Diagnosis Rate



(a) Aggregate



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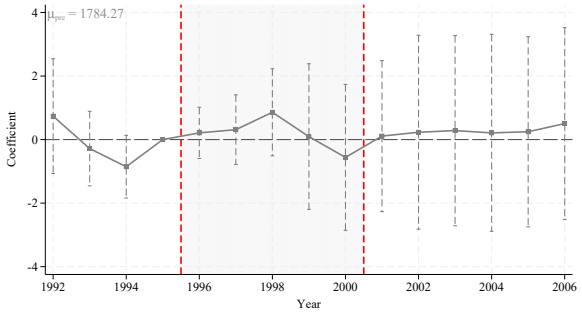

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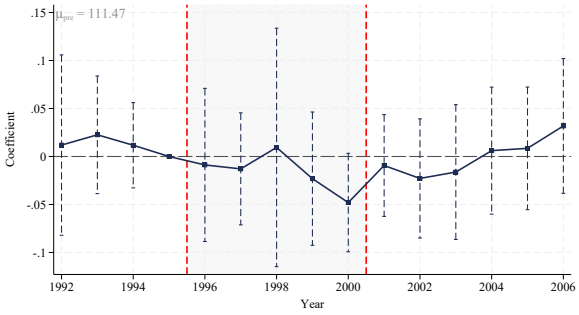

(d) Hispanic Only

Note: These figures show the triple-differences event study coefficients from equation 3 with the gonorrhea diagnosis rate as the dependent variable. Panel (a) shows the aggregate results, while panels (b)-(d) show the results for whites, blacks, and Hispanics, respectively. The mean of each dependent variable is shown in the top-left corner of each panel.