A NATIONAL ACTION PLAN FOR UNIVERSAL ACCESS TO HIV PRE-EXPOSURE PROPHYLAXIS (PrEP) IN THE UNITED STATES

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A White Paper from The PrEP4All Collaboration

The PrEP4All Collaborations is a group of grassroots activists whose aim is to end the HIV epidemic. We can do this today by increasing access to HIV PrEP as part of a biomedical model of epidemic control. We perform direct actions; we communicate with the public; and we develop strategy based on the latest scientific data.

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Forward

"Someday, the AIDS crisis will be over. Remember that. And when that day comes -- when that day has come and gone, there'll be people alive on this earth -- gay people and straight people, men and women, black and white, who will hear the story that once there was a terrible disease in this country and all over the world, and that a brave group of people stood up and fought and, in some cases, gave their lives, so that other people might live and be free."

Vito Russo

On April 12, 1955, the world learned that a safe and effective vaccine had been developed to protect against one of the most feared pathogens known to humanity, polio. That month, the then President of the United States, Dwight D. Eisenhower, directed the Department of Health, Education and Welfare to develop a national plan to distribute and administer the vaccine to as many people as possible. "I believe very greatly in the power that can be developed by the humanitarian agencies of this country when they work together in cooperation," Eisenhower remarked, assuring the nation that government, working alongside industry, will achieve "the most rapid possible distribution of this vaccine".[1]

Jonas Salk, the leader of the team that invented the vaccine, famously refused to patent it, remarking that it would be like "patenting the sun". Salk's decision enabled five separate pharmaceutical companies to simultaneously manufacture the vaccine, allowing it to be produced in both great quantity and at low cost. Armed with a plethora of low cost vaccines, Eisenhower asked Congress to appropriate $28 million dollars ($280 million in 2018 dollars) to ensure that the vaccine was available to everyone, regardless of their ability to pay. Finally, the President's administration orchestrated a coordinated response at every

[1]Dwight D. Eisenhower: "The President's News Conference," April 27, 1955. Online by Gerhard Peters and John T. Woolley, *The American Presidency Project*. http://www.presidency.ucsb.edu/ws/?pid=10462.

level of government across all fifty states to ensure that this life saving technology would reach Americans as soon as possible.[2]

Eisenhower and Salk's commitment to universal access to the polio vaccine paid off. In one of the most dramatic public health victories in human history, the number of new polio cases in the United States decreased by more than 92% within six years.[3] Less than three decades later, the polio virus would be eradicated from the United States.

On July 16, 2012, the United States Food and Drug Administration (FDA) announced the approval of Truvada—a fixed dose combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC)—for its use in preventing human immunodeficiency virus (HIV) infection. Known as TDF/FTC pre-exposure prophylaxis or "PrEP", the drug was the first drug approved to prevent rather than treat HIV infection. In the clinical trials that would be used to gain FDA approval, TDF/FTC PrEP proved highly efficacious, showing that in men who have sex with men (MSM) and transgender women daily use of the drug was associated with a ninety nine percent reduction in risk of HIV acquisition,[4] significantly more efficacious than the original results of the Salk Vaccine Trial.[5]

Like the polio virus before it, HIV is one of the deadliest scourges known to humanity. Since the first cases were reported in 1981, nearly 700,000 people in the United States and more than 35 million across the globe have perished in this modern plague. Despite this, our government did not rush to implement TDF/FTC PrEP. There were no presidential press conferences, no new Congressional appropriations, and the number of people starting TDF/FTC PrEP that year was less than one percent of the number of people who had indications for its use.[6]

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[2] Dwight D. Eisenhower: "Statement by the President on the Polio Vaccine Situation.," May 31, 1955. Online by Gerhard Peters and John T. Woolley, *The American Presidency Project*. http://www.presidency.ucsb.edu/ws/?pid=10247.

[3] Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington D.C. Public Health Foundation, 2015. https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/E/reported-cases.pdf

[4] PL Anderson et al., "Emtricitabine-tenofovir exposure and pre-exposure prophylaxis efficacy in men who have sex with men" *Sci Transl Med.* 2012 Sep 12; 4(151): 151ra125.

[5] Monto AS. "Francis Field Trial of Inactivated Poliomyelitis Vaccine: Background and Lessons for Today" *Epidemiol Rev.* 1999;21(1):7-23.

[6] Giler RM et al., "Changes in Truvada (TVD) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States: (2012-2016)" *IAS 2017 Paris* Abstract No. 1614

Today, more than six years after its approval by the FDA, the utilization of TDF/FTC PrEP in the United States remains abysmal, with less than ten percent of people with indications accessing it. The latest data from the Centers for Disease Control and Prevention (CDC) is sobering: 38,500 new HIV infections each year in the United States—more than four an hour—and nearly 7,000 people still die from it each year. People of color, transgender people, men who have sex with men, and women are at significantly higher risk of new infections compared to other Americans. While the country still lacks a comprehensive surveillance system for PrEP utilization, what little data we do have is disturbing. The dramatic disparities in access to and utilization of TDF\FTC PrEP are likely already exacerbating rather than mitigating these inequities.

America's success in fighting polio proves what is possible when our society dedicates itself to fighting for better health for all. Faced with more than a half decade of government inaction, we have come together as a group of activists—the PrEP4All Collaboration—to demand our government once again dedicate itself to grand programs because we are nowhere close to ending the epidemic in the US.

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Executive Summary

HIV pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) is the most effective method of HIV prevention for HIV negative persons known. Approved for use in the United States in 2012, when taken daily, TDF/FTC PrEP is more than 99% effective in preventing HIV infection.

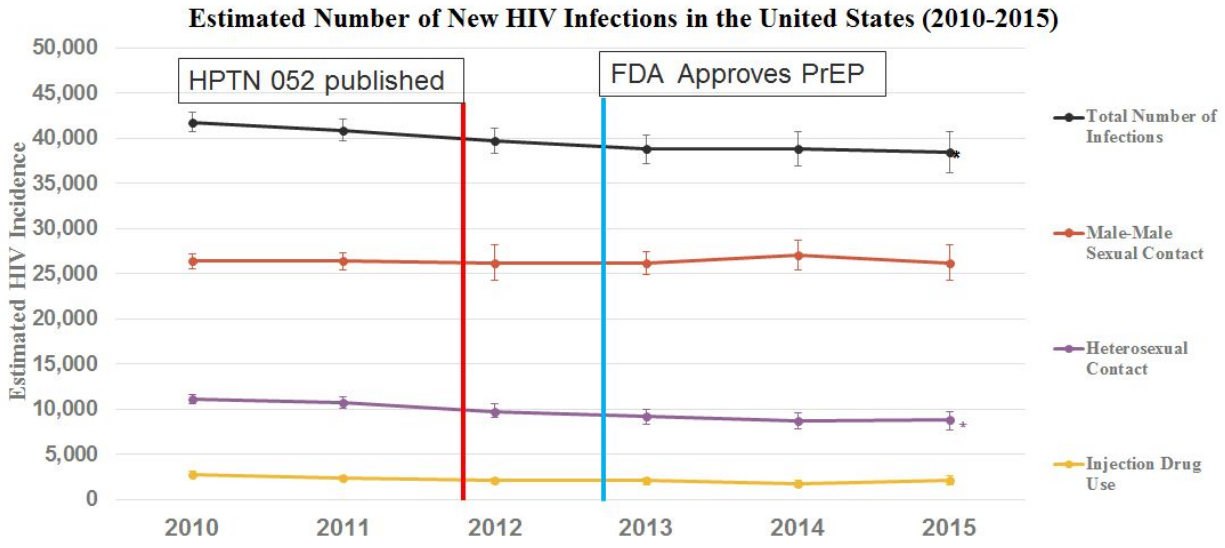
Despite its proven efficacy for both individuals and at population scale, the potential for TDF/FTC PrEP to dramatically decrease rates of HIV in the United States has not been fully realized. More than six years after FDA approval, utilization and access in the US remains abysmal. Less than ten percent of people with indications for PrEP are accessing it and major disparities along racial lines, geographic regions, and sex have already emerged. We believe the root cause of this problem is the price. Gilead Sciences, the manufacturer of the only domestically available version of TDF/FTC PrEP, charges in excess of $1,600 a month, despite FDA-approved versions of generic TDF/FTC costing less than $6 internationally, a markup of over 25,000%.
None of the research used to support the FDA approval of Truvada for its use as PrEP was meaningfully funded by Gilead but rather by the U.S. taxpayers via the National Institutes of Health (NIH), as well as by The Bill and Melinda Gates Foundation. Remaining patents on Truvada are based on research that was funded by taxpayers through federal grants.

This white paper was developed by a small group of HIV activists in New York City. The following document outlines our plan for universal PrEP access. This plan would provide free TDF/FTC and clinical care to every American who needs PrEP for a cost less than what our healthcare system currently spends to get PrEP to less than ten percent of the people who need it. In addition, this plan would provide over half a billion dollars a year to address systemic and individual barriers to PrEP access. In order for this to occur, the federal government needs to act, using existing law, to break the patents that enable Gilead's monopoly on TDF/FTC. We present this plan as a request for additional leadership and thought partners. How do you see a universal PrEP rollout affecting your community? How can we work together to end the HIV epidemic in the United States while also tackling non-cost related barriers to PrEP access? We welcome your leadership and input.

Introduction

Despite declines in national HIV incidence since 2000, almost 40,000 Americans become newly infected with HIV every year in this country.[7] For the last 5 years of reported data from the CDC, new HIV infections decreased only slightly from 41,800 (95% confidence interval: 40,800 – 42,900) in 2010 to 38,500 (95% CI: 36,200-40,700) in 2015 ($p < 0.05$).[8] Despite this small decrease, incidence in key demographic areas, especially in men who have with men (MSM), has not declined. When analyzed by race/ethnicity, incidence among white MSM appears to be declining significantly, black MSM incidence appears stable, and Hispanic\Latino MSM incidence is increasing. MSM, including those who inject drugs, continue to represent more than two-thirds of new HIV infections in the United States —27,400 per year in 2015 or more than three an hour—despite representing less than 3% of the U.S. population.[9]

Estimated Number of New HIV Infections in the United States (2010-2015)[1]



[7] Centers for Disease Control and Prevention. "Estimated HIV incidence and prevalence in the United States, 2010–2015." *HIV Surveillance Supplemental Report* 2018;23(No. 1).
[8] Ibid.
[9] Ibid.

Tremendous disparities continue to be reflected in the data: over half of all new U.S. HIV cases in 2015 were in the South and over two out of three new cases are in Black and Latinx\Hispanic Americans.[10] The national data also obscures different trends occurring on the state level over the last five years, with states in the New York tri-state area seeing decreases of roughly 20%, Texas and California remaining relatively stable, and Hawaii and Indiana seeing increases of over 60%. We do not have the epidemic under control in this country.

The relative stasis in moving the needle significantly towards the goal of zero new HIV infections over the last five years is made even more disappointing by the fact that it occurred during a period where two of the most important biomedical advances in HIV prevention became available: tenofovir disoproxil fumarate\ emtricitabine (TDF/FTC) pre-exposure prophylaxis (PrEP) and the discovery that people living with HIV who are durably virally suppressed have virtually no risk of forward transmission, commonly known as treatment as prevention (TasP) or undetectable = untransmittable (U=U). While we will discuss U=U briefly, the purpose of this whitepaper is to examine the gross underutilization of PrEP in the country and to identify impactful solutions.

Over 1.2 million Americans have an indication to be on PrEP based on the US Public Health Service PrEP guidelines[11]. Despite being on the market for over 6 years, a maximum of 117,000 people or less than 10% of those with indications are on it[12]. Furthermore, extreme racial, ethnic, geographic and gender disparities in access to and utilization of TDF/FTC PrEP exist, which, if not mitigated rapidly, will exacerbate the already egregious inequities that have been present in this epidemic since the first cases were reported.

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[10] Ibid.

[11] Smith DK et al., "Vital Signs: Estimated Percentages and Numbers of Adults with Indications for Preexposure Prophylaxis to Prevent HIV Acquisition — United States, 2015" *MMWR Morb Mortal Wkly Rep.* 2015 Nov 27;64(46):1291-5. doi: 10.15585/mmwr.mm6446a4.

[12] Siegler AG et al., "The prevalence of pre-exposure prophylaxis use and the pre-exposure prophylaxis-to-need ratio in the fourth quarter of 2017, United States." *Ann Epidemiol.* 2018 Jun 15. pii: S1047-2797. **NOTE**: The informed reader will note that this estimate differs from those commonly cited by e.g. Gilead earnings calls. Based on communications with public health researchers, Gilead employees, as well as published data and our own analysis of prescription data within the Symphony Health Solutions Integrated Dataverse (IDV), we have concluded that those higher estimates include all individuals who have ever *started* TDF\FTC PrEP, including those that are no longer actively taking the drug.

After reviewing the data of the first six years of PrEP scale-up in this country, our conclusion is clear; **the current low rate of PrEP utilization is one of the greatest public health implementation failures in the history of this country**.

This failure is multifactorial and the result of many known and persistent shortcomings in our healthcare system. However, we believe the greatest contributors to low utilization are:

- The failure of the United States Government to develop a comprehensive and coordinated plan to ensure that all Americans vulnerable to HIV infection can access TDF/FTC PrEP, as well as associated clinical care, regardless of their ability to pay.
- The failure of the healthcare system to recognize TDF/FTC PrEP as an essential public health tool, analogous to a highly effective daily oral vaccine. This resulted in a failure to educate the American public, as well as many healthcare providers, on the benefits and use of TDF/FTC PrEP. Furthermore, the myriad of federal health agencies failed to prioritize scale up of TDF\FTC in an effective, community-based, culturally-tailored manner.
- The failure of our healthcare system to research and implement population specific programs, like those piloted in HPTN 073, to make sure that vulnerable populations can access in TDF/FTC in an optimal context.
- The failure of our drug regulatory system, federal agencies and legal system in controlling Gilead Sciences' outrageously high price of Truvada – the only version of TDF/FTC commercially available in the United States. This resulted in billions of dollars being spent unnecessarily each year by the healthcare system to purchase Truvada, money that could of otherwise been spent in mitigating the multitude of other barriers to TDF/FTC PrEP.

In this whitepaper we aim to:

- Briefly review the data demonstrating the clinical effectiveness of PrEP.
- Highlight theoretical and real-world models that demonstrate PrEP can dramatically reduce HIV incidence at the population scale.
- Discuss a number of financial barriers for low utilization rate of PrEP in those with indications for use.

- Propose potential governmental and legal solutions to make PrEP widely available for a massive scale-up of PrEP utilization in the US.

While this white paper is focused on domestic issues and solutions around HIV PrEP, we look forward to working with our international family on future projects related to increasing access to PrEP so that we may end this global pandemic.

Furthermore, this white paper is a starting point. We welcome constructive criticism and thoughts from our readers and hope this starts a much-needed dialogue on how to offer PrEP to everyone in the US who needs it.

PrEP Is Extremely Effective at Preventing HIV Infection

The Efficacy Results of the Partners PrEP and iPrEx Trials Led to FDA Indication of HIV PrEP for TDF/FTC

The Partners PrEP study was one of two randomized control trials (RCTs) used by Gilead in obtaining an indication for HIV PrEP for TDF/FTC.[13] Funded by the Bill and Melinda Gates Foundation, the Partner PrEP Study was a three-arm RCT that randomized HIV-negative partners in serodiscordant heterosexual partnerships to either daily TDF, TDF/FTC, or placebo. The study was carried out in Kenya and Uganda and the HIV-positive partners were ineligible for antiretroviral therapy according to national guidelines. The primary end point was seropositivity in partners previously seronegative for HIV-1 with planned monthly follow-up for 36 months. Gilead did donate study drug, but did not otherwise fund the trial.

Partners PrEP enrolled roughly 1500 HIV-negative subjects into each arm. The trial was halted early due to superiority of both TDF/FTC and TDF for the primary endpoint, demonstrating 75% (95% CI, 55 to 87; p <0.001)and 67% efficacy (95% CI, 44 to 81; p<0.001), respectively, in preventing new HIV infections compared to placebo. Protective effects of TDF–FTC and TDF alone against HIV-1 were not significantly different (p = 0.23) . TDF/FTC was equally efficacious for men and women and adherence based on returned bottles and pills during follow-up visits was estimated at 92%. A detectable level of tenofovir, as compared with an undetectable level of the drug, was associated with estimated reductions in the relative risk of acquiring HIV-1 of 86% (with TDF) and 90% (with TDF–FTC).

The Preexposure Prophylaxis Initiative (iPrEx) trial was the second RCT used by Gilead to apply for a PrEP indication for TDF/FTC.[14] Funded by over $40 million investment from the American taxpayer through the National Institutes of Health (NIH)[15] and the Bill and Melinda Gates Foundation, the iPrEX trial randomized 2499 HIV-negative men and transgender women who have sex with men to TDF/FTC or placebo (Gilead Sciences

[13] Baeten JM et al. "Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women." NEJM. 2012; 367:399-410. DOI: 10.1056/NEJMoa1108524

[14] Grant RM et al. "Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men." NEJM 2010; 363:2587-99.

[15] Total cost exceeds $41,279,316 for NIH Spend on iPrEx Clinical Trial. See NIH Project Number U01AI064002 (" CHEMOPROPHYLAXIS FOR HIV PREVENTION IN MEN")

donated FTC–TDF and placebo tablets and provided travel-related support for meetings conducted by non-Gilead investigators). The primary outcome was efficacy in reducing new HIV infections.

iPrEx demonstrated that subjects taking TDF/FTC had a 44% overall reduction (95% CI, 15 to 63; *p*=0.005) in new HIV cases and that efficacy was strongly linked to drug adherence. By analyzing intracellular drug concentration, a proxy for medication adherence, the trial demonstrated very high rates of efficacy when the medication was taken regularly: 76% for two doses per week, 96% for four doses per week, and 99% for seven doses per week.[16]

It should be noted that **none of the research used to support Gilead's successful application to the FDA for a PrEP indication for Truvada was meaningfully funded by Gilead but rather by the U.S. taxpayers via the NIH, as well as by The Bill and Melinda Gates Foundation.**

PROUD and IPERGAY Trials Proved the Efficacy of TDF/FTC in HIV-Prevention in Real-World Settings

After the approval of PrEP by the FDA, doubts remained about the real-world effectiveness of PrEP due to possible issues with adherence, changes in sexual practices, and inability to target those most at risk. However, two well-designed studies in the UK and France, PROUD and IPERGAY, demonstrated that real world adherence was actually *higher* after the efficacy of PrEP had already been established, i.e., patients at high risk will seek out and take PrEP when they know it works.

The PROUD trial was an open-label, pragmatic wait-list trial that randomized 544 high risk HIV-negative MSM subjects in the UK to either daily TDF/FTC immediately or after a 1 year deferral period (TDF/FTC for PrEP was not and is currently not available on the English or Welsh National Health Service (NHS) or Health and Social Care in Northern Ireland,

[16] Anderson PL et al., "Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men" *Sci Transl Med*. 2012 Sep 12;4(151):151ra125.

however it is available on Scotland's NHS).[17] Participants receiving TDF/FTC had an **86%** reduction (90% CI 64–96, *p*=0.0001) in HIV incidence compared to those who were in the delayed group. Additionally, the high HIV incidence in the delayed group (9.0/100 person years) demonstrated the ability to target high-risk individuals. Fiscal sponsorship was provided by the U.K. MRC Clinical Trials Unit at UCL and Public Health England. Gilead provided minimal support in the form of drug and around £250,000 to carry out a pharmacokinetic substudy, additional diagnostics, and student funding[18].

The IPERGAY trial was a French trial investigating an on-demand approach to PrEP administration.[19] The study randomized 414 HIV-negative MSM participants to a four-pill regimen (two prior to sex and one daily for two days after) of either TDF/FTC or placebo. The trial was halted early due to a a high 86% efficacy (95% CI, 40 to 98; *p*=0.002) of TDF/FTC in preventing new HIV infections compared to placebo. The trial was funded by the French National Agency of Research on AIDS and Viral Hepatitis [ANRS].

A Large Cohort Study in the San Francisco Bay Area Demonstrates 100% Efficacy of PrEP in Real-World Setting with Good Adherence

A cohort of Kaiser Permanente insurance members who initiated PrEP between July 2012 and June 2015 demonstrated 92% adherence and no HIV seroconversions, i.e. an observed **100% efficacy**, during PrEP use.[20] However, people with high drug copayments had a statistically significant lower rate of drug adherence (adjusted risk ratio: 2.0; 95% CI:1.2 to 3.3, *p* = 0.005) and two individuals who lost insurance and discontinued PrEP seroconverted, demonstrating the importance of access to care and the difficulty in obtaining PrEP without insurance coverage. Concerningly, identifying as African American, being a woman, and substance abuse were associated with PrEP discontinuation.

[17] McCormack S et al., "Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial." *Lancet.* 2016 Jan 2;387(10013):53-60.
[18] Personal correspondence.
[19] Molinda J-M et al., "On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection." NEJM. 2015. 373;23 (2237-46).
[20] Marcus J et al. "Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation." J AIDS. 2016. 73;5: 540-546.

EPIC-NSW Provides a Population-Based Example on How Universal PrEP Access Can Dramatically Lower Rates of New HIV Infections

In 2016, the Australian state of New South Wales began an open-label implementation trial aiming to enroll all 3700 MSM estimated to be at high-risk of HIV by the end of that year[21]. Using 20 clinics across the state, they reached their enrollment in October 2016. One year later, there was only 1 new case of HIV in the cohort, and the total rate of HIV infections decreases state-wide by 35% and early HIV infections in MSM declined a shocking 44% in pre-trial and post-complete enrollment six-month comparison periods. Not only were the declines dramatic, the rate was the lowest half-yearly number of HIV infections ever document in NSW since surveillance began in 1985. This is even more impressive considering that New South Wales has already surpassed its UNAIDS 90-90-90 targets by approximately 2013 (See Figure).

PrEP and IV Drug Users

While no RCTs have been performed evaluating the efficacy of TDF/FTC for PrEP in IV drug users, the Bangkok Tenofovir Study investigated the efficacy of TDF monotherapy in this population and found efficacy of 49% for all and 70% for those with any detectable tenofovir in their plasma at time of seroconversions.[22] Thus TDF/FTC should be an effective PrEP strategy in this population as well.

PrEP and HIV Treatment Work Hand-in-Hand

The Partners PrEP Demonstration Project showed that integrated delivery of PrEP and ART virtually eliminates incident HIV in serodiscordant couples.[23] In this study, PrEP was utilized

[21] Grulich A et al. Rapid Reduction in HIV Diagnoses after Targeted PrEP Implementation in NSW, Australia. http://www.croiconference.org/sessions/rapid-reduction-hiv-diagnoses-after-targeted-prep-implementation-nsw-australia

[22] Choopanya K et al. " Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial." Lancet. 2013 Jun 15;381(9883):2083-90.

[23] Integrated delivery of PrEP and ART results in sustained near elimination of HIV transmission in African HIV serodiscordant couples: Final results from the Partners Demonstration Project.

as a bridge to treatment and undetectability. PrEP was maintained for 6 months while the partner living with HIV was suppressed (i.e. durable viral suppression) and stayed that way for 6 months, at which point PrEP was discontinued. The only seroconversions were seen were when both the HIV-positive partner and HIV-negative partner elected not to take medications. By showing the elimination of new HIV infections whether the couple was on PrEP alone, started PrEP and ART at the same time, or used ART alone demonstrates the synergies of PrEP and U=U.

TDF/FTC PrEP Has a Low Side Effect Burden

PrEP is generally well tolerated and only approximately 2% of users discontinued due to side effects, mostly abdominal discomfort.[24] While TDF has been associated with nephrotoxicity (kidney damage) in HIV-infected patients, the data from PrEP clinical trials is more reassuring. In the IPERGAY and Partners PrEP studies, neither trial found a meaningful change in kidney function in PrEP users compared to placebo. The iPrEx trial found a small but statistically non-significant change in the percentage of individuals with worsening renal function. We do note, however, that TDF related renal abnormalities are often not detected during clinical trials[25], instead they are often detected during "real world practice". Additionally TDF has been associated with decreased bone mineral density, but this is not clinically significant in most cases and is reversible. The rates of bone fractures were similar between TDF/FTC and placebo groups in the iPrEx and IPERGAY trials.

The Low Rate of PrEp Utilization Is One of the Greatest Public Health Implementation Failures in the History of This Country

In 2015, the CDC published a report estimating that 1.2 million, and potentially up to 1.8 million, people in the US have indications for PrEP (based on 2014 U.S. Public Health Service's PrEP guidelines).[26] However, that year, only 77,000 people filled at least one prescription for PrEP, roughly 6% of those who should have been.[27] Current estimates are

[24] Grant RM et al. "Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men." NEJM 2010; 363:2587-99.
[25] Atta MG, Fine DM. "Editorial comment: Tenofovir nephrotoxicity-the disconnect between clinical trials and real-world practice" *AIDS Read.* 2009 Mar;19(3):118-9.
[26] Smith DK et al. "Vital Signs: Estimated Percentages and Numbers of Adults with Indications for Preexposure Prophylaxis to Prevent HIV Acquisition — United States, 2015". MMWR. 2015;65(46);1291-1295.
[27] AIDSvu 2016 data

that 109,000 people received PrEP in 2017, or roughly 8% of those with indications.[28] While PrEP usage grew quickly between 2014-2015, the number of new prescriptions has stabilized since 2016 with under 4,000 new prescriptions monthly.[29] At that rate, it will take over 22 years to get the 1.1 million additional people who should be on PrEP on it.

When you compare the rate of PrEP uptake in those with indications, it is drastically lower than the national rates of vaccination, even when such vaccination is voluntary. Roughly 60% of US adolescents had received at least one dose of the voluntary HPV vaccination in 2017. Males have only had indications for HPV vaccination since 2011 and have already achieved vaccination rates of over 50%. For influenza, an annual vaccination, the rate for voluntary vaccination by adults was 47% for 2017-18.[30] Thus rates of PrEP uptake in the US, at around 6% of those with indications, are an order of magnitude lower than those for voluntary vaccine programs in adults.

When pursuing a status neutral approach to HIV care, it is also important to compare the rates of PrEP use in those with indications to the rates of ART use or viral suppression in those who are HIV-positive.[31] Nationally, 57.9% of people living with HIV were virally suppressed with a target rate of 80% by 2020. We advocate for a similar target, 80%, for 2020 for PrEP utilization in those with indications. The CDC should follow and track these numbers regularly, and should report them as a percentage of those with indications, not as a whole number, in order to demonstrate progress, or in the current situation, the lack thereof. Additionally, the CDC should report quarterly numbers of PrEP use (prescription numbers) for use by other government agencies, researchers and activists.

Despite Low National Rates of PrEP Utilization, Significant Disparities Have Already Emerged

Not only are most people who should be on PrEP not on it, there are significant disparities already emerging in PrEP use in the US. According to the CDC, from September 2015 to

[28] Mera R et al., "Changes in Truvada for HIV Pre-exposure Prophylaxis Utilization in the USA 2012-2016. 19th IAS Conference on HIV Science.
[29] Ibid
[30] Fluvax View. https://www.cdc.gov/flu/fluvaxview/nifs-estimates-nov2017.htm
[31] Myers JE et al. "Redefining Prevention and Care: A Status-Neutral Approach to HIV". Open Forum Infectious Diseases, Volume 5, Issue 6, 1 June 2018.

August 2016, while roughly 14% of Whites with PrEP indications were on it, only 1% of African Americans and 3% of Latinos with PrEP indications had prescriptions.[32] Significant geographic disparities also exist. While half of all new cases of HIV are in the South, the region only accounted for 30% of all PrEP prescriptions in 2016.[33] Additionally, the Northeast has roughly twice the rate of PrEP use (47.4/100,000) compared to the South (22.6/100,000), the Midwest (23.5/100,000) and the West (28.1/100,000)[34]. There are huge sex disparities as well: 14 times as many men are on PrEP as women despite women accounting for almost 1/3rd of those with PrEP indications nationally (ie, only 2 times as many men should be on PrEP as women).[35,36]

How Effective Could PrEP Be in Helping to End the HIV Epidemic in the US?

Due to the high price of TDF/FTC, most studies looking at the impact of PrEP in reducing HIV incidence have focused on cost-effectiveness models to guide PrEP implementation strategies.[37] While placing every sexually active American on PrEP could lead to HIV incidence rates approaching zero, this is not a practical consideration and is unnecessary. However, PrEP uptake approaching 90% within certain high-risk populations could lead to dramatic reductions in incidence. One model looking at reduction of HIV incidence in New York City estimated that with PrEP efficacy of 75% and PrEP uptake of 90% in the MSM population, overall new HIV cases would be reduced by 47%.[38] The similarity between this estimate and what was achieved in NSW should be noted.

New York City Is One Example of Real World PrEP Effectiveness in The U.S.

[32] Smith DK et al. CROI 2018 Presentation.
[33] AIDSvu PrEP Data 2018 Launch Toolkit.
[34] Ibid
[35] Ibid
[36] Smith DK et al. "Vital Signs: Estimated Percentages and Numbers of Adults with Indications for Preexposure Prophylaxis to Prevent HIV Acquisition — United States, 2015". MMWR. 2015;65(46);1291-1295.
[37] McKenney J et al. "Optimal Costs of HIV pre-exposure prophylaxis for men who have sex with men." PLOS One. 2017. https://doi.org/10.1371/journal.pone.0178170
[38] Kessler J et al. "Evaluating the impact of prioritization of antiretroviral pre-exposure prophylaxis (PrEP) in New York City." *AIDS.* 2014 Nov 28;28(18):2683-91.

Due to its high rates of viral suppression and active public health system, New York City has seen steady declines in HIV incidence since 2001. By promoting and distributing PrEP to achieve utilization rates that are roughly 20 times the national average, New York City saw its largest year over year percentage decline in HIV incidence since 2001 from 2015 to 2016: a decrease in HIV incidence of 8.6% in the total population and a steep 14.8% decline in men who have sex with men.[39] The extremely high rates of PrEP utilization in New York City should be emphasized here. While approximately 25/100,000 Americans were on PrEP in 2016, approximately 418/100,000 New Yorkers were on PrEP, including over 1% of all men in the city.[40] Rates in youth were even higher, with approximately 2.3% of all New Yorkers age 18-29 on PrEP (2,297/100,000). This decline can be attributable to the New York City Department of Mental Health and Hygiene's (DOHMH) biomedical model of HIV prevention which includes medications for those with HIV and PrEP for those at risk of acquiring it.[41] Thus by achieving a high rate of viral suppression in its citizens (over 75%) and high rates of PrEP use, New York City has seen continued and declines in new HIV diagnoses in a population with a substantial number of those most at risk. However, data from EPIC-NSW states that we could be doing dramatically better. We should attempt to reach every person at highest risk of HIV infection, just as they did in NSW***. But what would be the cost of such a program in the US?***

The PrEP Pricing Problem

TDF/FTC is a very cheap drug to manufacture. Globally, generics produce a **month's supply of TDF/FTC for less than $6[42], including a sizeable profit margin for generic manufacturers.**[43] Most of these generic suppliers produce TDF/FTC in FDA approved cGMP facilities, to supply ARVs to PEPFAR at low unit prices. According to the Pan American Health Organization (PAHO), TDF/FTC is available for purchase through the PAHO Strategic Fund for $5.25 per bottle as of December 2017. Brazil has also rejected Gilead's patent

[39] HIV Surveillance Annual Report, 2016. New York City Department of Health and Mental Hygiene.
[40] Trends and Associations with PrEP Prescription among 602 New York City (NYC) Ambulatory Care Practices, 2014-16. https://idsa.confex.com/idsa/2017/webprogram/Paper63138.html
[41] Myers JE et al. "Redefining Prevention and Care: A Status-Neutral Approach to HIV". Open Forum Infectious Diseases, Volume 5, Issue 6, 1 June 2018.
[42] Hill AM, Pozniak AL. "How can we achieve universal access to low-cost treatment for HIV?" *Journal of Virus Eradication*. 2016;2(4):193-197. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5075345/
[43] Personal Correspondence with D. Ripin, Clinton Health Access Initiative (CHAI)

application making TDF/FTC significantly more affordable, at around 75 cents a pill or $23 for a month's supply. This is directly contributing to Brazil's plans to dramatically make PrEP free to eligible individuals through their public health clinics.[44] For the first year of the program, the Health Ministry spent just $2.7 million for 3.6 million pills. It stands to become even cheaper as generic versions arrive to market this year.

Why Is Truvada So Expensive in the United States?

In the United States, Gilead maintains a monopoly on Truvada. Truvada consists of two drugs in a fixed dose combination (FDC): tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). TDF's patent protection expired in early 2018.[45] All the patent protection on the FTC *molecule* have already expired. However, the use of the levorotatory (-) enantiomer of FTC – rather than racemic FTC -- is still protected by two patents until 2021.[46] [47] [48] **The intellectual property on these patents are products of federally funded research and thus subject to March-In Rights and other governmental rights pursuant to the Bayh-Dole Act.**[49]

Gilead Is Likely Engaging in Illegal "Pay for Delay" Settlements

Additionally, it is unlikely that a patent on the use of a single enantiomer of a nucleoside analogue– especially considering that the use of that purified enantiomer was suggested in proceeding patents -- would be considered valid after court challenge. In fact, seven generic drug manufacturers have declared that they believe the patents are invalid pursuant to "Paragraph IV" of the Hatch-Waxman Act.[50] Despite extensive litigation, Gilead has settled all these patent disputes prior to a court being able to issue a decision on the validity of these patents. This pattern of settlements is consistent with illegal "pay for delay"

[44] https://www.nytimes.com/2017/12/12/world/americas/prep-brazil-hiv-aids.html
[45] This can be seen by searching the Food and Drug Administration's "Orange Book" listing for N021752.
[46] Ibid.
[47] U.S. Patent No. 6,642,245
[48] U.S. Patent No. 6,703,396
[49] Ibid.
[50] 21 U.S.C. §355(j)(2)(A)(vii)(IV).

settlements.[51] The Federal Trade Commission should open up investigations relating to potential illegal attempts to "evergreen" these patents.

The Price for TDF/FTC in the United States is Vastly Inflated

In the United States, the National Average Drug Acquisition Cost for a 30 days supply of Truvada, i.e. the price to the healthcare system, **exceeds $1,600** for a month's supply, **a year's supply cost exceeds $19,000** as of May 2018**.**[52] Total aggregate spending on TDF/FTC for PrEP in the US annually is not known. However, according to Gilead Sciences latest 10-Q, annual revenue from Truvada sales in the United States will exceed $2 billion in 2018[53]. Note that the actual spend to the healthcare system is, without doubt, much higher, because this does not include wholesaler fees, distribution costs, pharmacy benefit manger fees, or pharmacy related costs, all of which are *in addition* to the revenue Gilead receives. Furthermore, because of the introduction of FTC/Tenofovir Alafenamide Fumarate (TAF) (Descovy) based HIV treatment regimens, as well as the increasing popularity of single tablet regimens, it is likely that the vast majority of Truvada's revenue is from its use as PrEP. At best estimate, approximately 109,000 people were on TDF/FTC for PrEP in 2017.[54] At the NADAC price, that is a $2.1 billion cost to the US healthcare system; if all 1.2 million with PrEP indications took PrEP daily, the cost would be $23 billion per year.[55] The National Health Expenditure Accounts estimate for the total cost of prescription medications in the US in 2016 was $329 billion; $23 billion would be equivalent to 7% of the total prescription expenditures for the country.[56] It is simply inconceivable for coverage systems to sustain that sort of annual spending for one regimen; the clear incentive is for public and private payers to under-promote PrEP and ration access.

[51] Silverman E. "AIDS activists urge N.Y. attorney general to probe Gilead for antitrust violations". *STAT News* . URL: https://www.statnews.com/pharmalot/2017/08/29/aids-ny-gilead-antitrust/

[52] https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-as-of-2018-05-09/5d2q-nmyv

[53] Gilead Sciences., Inc. "QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 For the quarterly period ended March 31, 2018"

[54] http://www.croiconference.org/sites/default/files/posters-2018/1430_Siegler_1022LB.pdf

[55]http://www.croiconference.org/sessions/raceethnicity-blacks-have-highest-number-needing-prep-united-states-2015

[56]https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsHistorical.html

By comparison, at $70/year the total cost would be **$84 million** for every single person with a PrEP indication to be on Truvada, reducing it to 0.02% of 2016 national prescription spending. This would dramatically change the calculus for coverage entities and be more on par with other essential preventive health services, such as the flu vaccine. It costs approximately $20 to administer the flu vaccine, and, as such, the US vaccinated 145 million people against flu in 2015 for under $300 million.[57]

PrEP Functions as a Daily, Oral Vaccine and Should Be Priced Similar to Other Vaccines to End the HIV Epidemic

TDF/FTC, despite functioning as an oral daily vaccine, is orders of magnitude more expensive than what private payers pay for vaccines. HPV vaccination with Gardasil®9 is the most expensive vaccination series administered today. At $204.87 per dose, the entire 3 dose series costs approximately $600 and confers lifetime protection. Other rates per dose of vaccines for adults include Hepatitis A (~$60/dose), Hepatitis B (~$50/dose), and Influenza (~$20/dose). Even newly developed vaccines with strong marketing campaigns such as that for the updated shingles vaccine (Shingrix) cost around $200/dose. At a National Average Drug Acquisition Cost of roughly $19,000 a year, a single pill of Truvada costs the same as each Hepatitis vaccine and twice as much as the flu vaccine. We will argue that the government needs to take a public health approach similar to vaccination, should report PrEP utilization rates along with those of other adult vaccinations, and its use should be addressed by the CDC Advisory Committee on Immunization Practices. Additionally, as argued below, we believe the government should invoke one of its rights under Bayh-Dole or 28 U.S.C. § 1498(a) to properly fulfil its governmental duties to protect its citizens by contracting with generic manufacturers to supply generic PrEP for public health use.

The High Cost of TDF/FTC Deters Health Systems from Scaling up PrEP Use

[57] National Immunization Survey-Flu (NIS-Flu) and Behavioral Risk Factor Surveillance System (BRFSS). Available at https://www.cdc.gov/flu/fluvaxview/coverage-1516estimates.htm

The artificially high price of Truvada has **real world impacts on the ability of individuals to access PrEP.** As mentioned previously, from a coverage-level perspective, high prices de-incentivize coverage for public and private payers, meaning that community members and community based organizations must use their limited time and resources to advocate for access to Truvada. A 2016 European Centre for Disease Prevention and Control (ECDC) survey of 32 European health ministries found that cost was the number one barrier to scale up, with 31 countries listing it as an issue and 24 countries rating it as an issue of high importance.[58] Cost greatly overshadowed any other potential barrier, including concerns about adherence, potential risk compensation, and feasibility of scale up. We are unaware of a comparable survey of American private and public coverage entities. While this is a European and not an American survey, we can safely assume that if cost is considered a major barrier and disincentive to scale up among European payers, it is probably also a disincentive to American coverage entities. This notion– that high price leads to poor coverage– is obvious, but somehow gets lost within the discussion of PrEP scale up in the US.

Advocates in England have long been aware that the National Health Service's refusal to cover PrEP– which was overwhelmingly validated by the PROUD study's stunning 86% reduction in new infections among English gay men taking PrEP– is directly tied to the enormous price of the medications.[59] A 2017 analysis of cost effectiveness by Public Health England found that the budgetary impact of even a modest program was considerable: in a single year, a PrEP service for 5,000 PrEP person years would cost €36.6M (£26.9M) at the current British National Formulary (BNF) price of the patented drug.[60] From a UNAIDS discussion of the PHE analysis: "[s]ince the price of the PrEP medicine is the main budgetary cost, it is crucial that ways be found to reduce this if PrEP programmes are to go to scale. Different funding models for PrEP have been explored, depending on country health programme frameworks, but the price of the PrEP medicine limits how many people will be offered it whether funding is central, through insurance programmes or private." [61]

[58]https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/pre-exposure-prophylaxis-hiv-prevention-europe.pdf

[59] McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet. 2016;387(10013):53-60. 10.1016/S0140-6736(15)00056-2

[60] https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.42.17-00192

[61] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5710114/

At Current Prices, It is Cheaper to Let People Get HIV than to Scale-Up PrEP

We developed a simple, quasi-static mathematical model to estimate the average cost of averting an HIV infection with PrEP in the US. Assuming a baseline HIV incidence of 2.0 per 100 person-years (a fairly high-risk group) and annual TDF/FTC price of $16,260 dollars (assumes some rebating from published drug acquisition prices), we found the average cost per annual infection averted was $986,041. Given a lifetime HIV treatment cost of roughly $438,994 in 2018 dollars, the healthcare system loses $547,047 for every HIV infection it prevents with PrEP, even in high incidence communities. Clearly, efforts to distribute PrEP at lower cost should be explored so that PrEP becomes cost saving to the healthcare system.

PrEP is the only evidence-based, highly effective primary prevention tool for HIV. A primary prevention tool should be cheap. If we hope to end the HIV epidemic in this country, or even dramatically reduce HIV incidence, we need dramatically lower prices for TDF/FTC.

Large Insurance Networks and National Healthcare Systems Are Faced with a Challenging Task to Cover Truvada for PrEP

Within the US, private insurers are similarly discouraging and delaying PrEP scale up, presumably due to cost. Advocates have had to push back against United Healthcare, Publix, and Assurant Health for denying PrEP coverage and imposing burdensome prior authorization requirements designed to limit access.[62] [63] [64] Unfortunately, the complexity of the US healthcare system means that these are only the cases we know about and may not indicate all of the challenges potential PrEP users are having with private insurers. While we may to some degree fault payers for not covering or de-incentivizing PrEP uptake, a

[62] https://www.nbcnews.com/feature/nbc-out/united-apologizes-reverses-truvada-policy-after-hiv-activists-push-back-n789801

[63] https://www.advocate.com/hiv-aids/2018/2/06/publix-reverses-will-begin-covering-prep

[64] https://www.poz.com/article/assurant-ends-prep-27179-3406

potential $25 billion annual national price tag for full PrEP scale up is understandably concerning to insurers.

Truvada for PrEP is reportedly one of the top 10 most expensive drugs in the US market in terms of spending, even though the use of it is less than desirable, putting pressure on formularies to deeply consider its inclusion. In 2018 alone Gilead Sciences, the drug's manufacturer, increased the price tag on the medication by 10%, which triggered insurers to impose barriers, like pre-authorizations, and consider not allowing manufacturer's co-pay card amounts to be used towards deductibles.[65] Governments that oversee nationwide healthcare systems, such as France and the UK, are faced with a plethora of tough decisions to make when assessing feasibility to roll out the intervention to their populations; a recent analysis puts the cost of providing PrEP at odds with the cost of providing lifelong HIV medication in the United States, the cost being the main driver of the effect.[66] [67] [68]

Gilead's Financial Assistance Programs are Inadequate

For Truvada, Gilead does provide two programs that supposedly help ameliorate the impact of high cost for individuals. The Medication Assistance Program (MAP) allows uninsured individuals with income below 500% of the federal poverty level (FPL) to receive the medication for free. The utilization of this program is unknown, however; despite repeated requests from advocates, Gilead refuses to provide MAP uptake data. We might presume that it is low, given that lack of insurance in most cases will mean that individuals cannot afford the doctors visits and quarterly lab work required of PrEP users.

The second program, Advancing Access, Gilead's Copay Assistance Program (CAP), address underinsured individuals by assisting with the large copays and deductibles required to obtained Truvada. The program is woefully insufficient given the high cost of Truvada. Advancing Access only covers $4,800 in out of pocket costs, and until recently, was only

[65] Some Health Plans Are No Longer Counting Gilead's PrEP Copay Cards Toward Deductible. Available at: http://www.thebody.com/content/80906/some-health-plans-are-no-longer-counting-gileads-p.html.
[66] France approves PrEP. Available at: http://www.aidsmap.com/France-approves-PrEP/page/3016707/
[67] Prep: HIV 'game-changer' to reach NHS in England from September. Available at: http://www.bbc.com/news/health-40814242
[68] Internal analysis submitted to IAC by Krellenstein et al.

$3,600 per year. It was only because of sustained pressure from advocates the even this small victory was achieved.

The Cost of Truvada Can Be a Significant Burden on Insured Consumers, Even When Support is Provided

Even at this increased amount, the CAP remains well below the out of pocket maximums established by the Patient Protection and Affordable Care Act (ACA) of $7,150 for individual plans and $14,300 for family plans. Thus many individuals on commercial health plans are forced to pay out of pocket costs of almost $10,000 per year to access Truvada or rely on some third-party payment support mechanisms with restrictive financial qualification criteria to pay these out of pocket costs. In an untold number of cases it simply means that people in need of PrEP will not access Truvada at all, substantially increasing their risk of HIV infection.

Accessing Healthcare Should Be Free of Barriers to Achieve Best Outcomes

So much of the experience in healthcare is shaped by direct interactions with healthcare workers including pharmacy technicians, providers, call center operators and other types of professionals; a negative experience at any point of contact could have a devastating impact on a patient. It is impossible to quantify how such experiences of denials, rejections or even conditional requirements, like pre-authorizations, impact one's ability to follow through with treatment. One must look no further than the recently barrage of testimonials and uproar following United Healthcare's then-decision to deny PrEP to consumers, based on a stigmatizing yet appropriate ICD-10 code for "High-Risk Homosexual Behavior."[69] Additionally, administrative hurdles, like Prior-Authorization requirements, delay drug initiation, continuation, and place challenges on prescribers and consumers.

[69] . *Insurer Apologizes For Shaming Man's "High Risk Homosexual Behavior" In PrEP Coverage Denial Letter. http://www.newnownext.com/insurer-apologizes-for-shaming-mans-high-risk-homosexual-behavior-in-prep-coverage-denial-letter/08/2017/

The Case for Government Action and a National PrEP Access Program

"The fight against infantile paralysis (polio) cannot be a local war. It must be nationwide. It must be total war in every city, town and village throughout the land. For only with a united front can we ever hope to win any war."

-Harry S Truman

The Need for a National PrEP Program

As detailed above, uptake of TDF/FTC PrEP over the last six years has been slow, uneven and hampered by numerous barriers. The results seen in the few locales with high uptake of TDF/FTC PrEP, however, demonstrate that TDF/FTC PrEP can be a successful *public health* intervention, quickly reducing the number of new HIV infections on a population scale. Our nation's previous successes—from the eradication of polio to the countless lives saved each year by current immunization programs—prove that highly effective control of infectious diseases can be achieved in the American healthcare system *if* a sufficient commitment from our government exists. A similar commitment must be made for HIV prevention—increased utilization of HIV PrEP must become a national priority. The federal government must implement a robust national PrEP plan, coordinated with state and local governments, to ensure that the benefits of PrEP use can be enjoyed by everyone nationwide, and not just the few locations and populations who are utilizing it sufficiently today.

Faced with more than half a decade of government inaction, we have developed a "first draft" outline of such a plan. It is important to note that this plan is a work in progress. We recognize we have almost certainly missed vital perspectives or insights, and we strongly encourage those with comments, concerns or questions to reach out to us.

Any plan which realistically hopes to dramatically expand PrEP utilization must focus on dramatically reducing the cost of TDF/FTC in the United States. While many readers may find this surprising, our analysis is clear: failure to reduce the price of TDF/FTC will require

expenditures and order of magnitude greater to achieve the exact same outcomes. We believe that the myriad of barriers to TDF/FTC PrEP utilization—even those which are not directly related to cost—can be mitigated through programmatic interventions. However, successfully implementing these interventions will require non-trivial financial expenditure. Every unnecessary dollar spent by the healthcare system to procure TDF/FTC is money that not spent on mitigating other obstacles to PrEP access and utilization.

We believe that the amount of money that our healthcare system *currently* spends on TDF\FTC PrEP—estimated to be roughly $2 billion per year—is sufficient to ensure: 1) nearly universal access to TDF/FTC PrEP in the United States; 2) associated clinical care including provider visits and laboratory testing; 3) a national marketing campaign to increase awareness; and 4) generous programmatic grants to community organizations to address a host of other barriers. However, such a program is only affordable *if* we reduce the cost of Truvada to near international generic pricing.

We believe that any effective National PrEP Program must ensure that:

- **All Americans vulnerable to HIV infection can easily access TDF\FTC PrEP and associated clinical care, regardless of their ability to pay or their insurance status.**

  The United States lacks a universal healthcare system—with approximately 15.5% of adults (age 19 to 64) lacking any healthcare coverage at all.[70] Unfortunately, many States with high rates of new HIV infections and populations most vulnerable to HIV acquisition also have some of the lowest rates of insurance coverage.[71] It is imperative that lack of health insurance or the inability to pay for any component of PrEP care should never prevent individuals from protecting themselves from HIV acquisition. Currently, lack of adequate access to healthcare is one of the most

[70] Collins SR et al., "First Look at Health Insurance Coverage in 2018 Finds ACA Gains Beginning to Reverse: Findings from the Commonwealth Fund Affordable Care Act Tracking Survey, Feb.–Mar. 2018," To the Point (blog), Commonwealth Fund, May 1, 2018.
[71] Marks SJ et al., "Potential Healthcare Insurance and Provider Barriers to Pre-Exposure Prophylaxis Utilization Among Young Men Who Have Sex with Men." *AIDS Patient Care STDS.* 2017 Nov;31(11):470-478

common and significant barriers to TDF\FTC PrEP use,[72] [73] [74] with one study finding those who lack insurance coverage to be four times less likely to access PrEP services compared to others.[75] In fact, in a survey of MSM and transgender women vulnerable to HIV infection, not having to pay for PrEP, access to free HIV testing, and access to free sexual health monitoring and clinical care while on PrEP were the three factors considered most important by community members in facilitating PrEP use.[76] Furthermore, insurance coverage issues were one of the most common reasons young MSM discontinued PrEP.[77]

- **Healthcare providers are aware of and willing to prescribe PrEP. Special attention should be focused on providers who are most likely to see patients vulnerable to HIV infection. Active interventions must be taken to reverse racial and ethnic bias in PrEP prescribing and to ensure prescribing occurs in a culturally sensitive manner.**

  Another significant barrier to PrEP access is that the healthcare providers most trained and willing to provide PrEP, HIV specialists, often do not see HIV negative patients.[78] Since potential PrEP patients are not living with HIV, primary care providers (PCPs) and urgent care/emergency department providers are the most likely to encounter those in need of PrEP. However, many PCPs express unwillingness to prescribe PrEP, based on unfamiliarity with prescribing antiretrovirals, uncomfortableness in discussing sexual activities, and concerns

[72] Pinto RM et al. "Improving PrEP Implementation Through Multilevel Interventions: A Synthesis of the Literature." *AIDS Behav*. 2018 Jun 5.
[73] Kelley CF et al., "Applying a PrEP Continuum of Care for Men Who Have Sex With Men in Atlanta, Georgia" *Clin Infect Dis.* 2015 Nov 15; 61(10): 1590–1597.
[74] Ojikutu BO et al., "Facilitators and Barriers to Pre-Exposure Prophylaxis (PrEP) Use Among Black Individuals in the United States: Results from the National Survey on HIV in the Black Community (NSHBC)" *AIDS Behav.* 2018 Feb 21
[75] Patel RR et al., "Impact of insurance coverage on utilization of pre-exposure prophylaxis for HIV prevention" *PLoS One*. 2017; 12(5): e0178737
[76] Golub SA et al. "From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City". *AIDS Patient Care STDs*. 2013;27(4):248–254.
[77] Morgan E et al., "High Rate of Discontinuation May Diminish PrEP Coverage Among Young Men Who Have Sex with Men" *AIDS Behav.* 2018 May 4.
[78] Krakower D et al., "HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care settings: a qualitative study." *AIDS Behav.* 2014 Sep;18(9):1712-21.

about complex insurance barriers to TDF/FTC access.[79] This unfamiliarity or unwillingness to provide PrEP results in "missed opportunities": patients at significant risk for HIV infection interact with the healthcare system frequently but are not prescribed PrEP and eventually acquire HIV.[80] Disturbingly, a survey of medical students observed statistically significant racial bias in a cohort of simulated PrEP patients, showing that future prescribers were less likely to prescribe PrEP to black compared to white patients.[81]

- **Awareness of TDF/FTC PrEP and HIV acquisition risk among vulnerable populations is increased. Special attention should be payed to ensure increased awareness and more accurate personalized risk-assessment in racial and ethnic minorities, transgender people, heterosexual women and people who inject drugs (PWIDs).**

  A key component of the fight against HIV/AIDS has been individual empowerment. Within the context of PrEP, awareness of its mere existence is the first step to individual empowerment. Yet for some of the most vulnerable populations, awareness regarding PrEP is extraordinarily low. For example, in a multi-city survey of black men and transgender women who have sex with men, a population with a HIV prevalence exceeding twenty five percent, less than forty percent of people surveyed were aware of PrEP.[82] In New York City, a survey of high-risk heterosexual women of color showed awareness was even lower, with only twenty five percent aware of PrEP.[83] In women who inject drugs, awareness was also low, with only a

[79] Petroll AE et al., "PrEP Awareness, Familiarity, Comfort, and Prescribing Experience among US Primary Care Providers and HIV Specialists" *AIDS Behav.* 2017 May; 21(5): 1256–1267.
[80] Smith DK et al., "Missed Opportunities to Prescribe Preexposure Prophylaxis in South Carolina, 2013-2016." *Clin Infect Dis.* 2018 May 22. doi: 10.1093/cid/ciy441
[81] Calabrese SK et al., "The Impact of Patient Race on Clinical Decisions Related to Prescribing HIV Pre-Exposure Prophylaxis (PrEP): Assumptions About Sexual Risk Compensation and Implications for Access" *AIDS Behav.* 2014 Feb;18(2):226-40.
[82] Eaton LA et al., "A multi-US city assessment of awareness and uptake of pre-exposure prophylaxis (PrEP) for HIV prevention among Black men and transgender women who have sex with men" *Prev Sci*. 2017 Jul; 18(5): 505–516.
[83] Gandhi A et al.,"PrEP Awareness, Interest, and Use Among Women of Color" IAPAC Conference, 2017 Abstract No. 378

third of women who injected drugs aware of PrEP.[84]

- **PrEP utilization is monitored in near real-time through a National Chemoprophylaxis Surveillance System (NCSS), which would provide weekly information about the number of people using TDF\FTC PrEP nationwide.**

  From a programmatic perspective, a large barrier to adequate PrEP scale up is the lack of data regarding its use. While multiple nationwide datasets exist to help answer this question, only one (AIDSVu) is publicly available. Additionally, there are enough significant limitations of that dataset to make it insufficient for national planning purposes. An adequate PrEP scale up will require high resolution (i.e. geographic, demographic, and utilization information) data on real world PrEP use to be publicly available. Such data is essential to public health officials, clinicians, activists, and academicians to monitor PrEP scale up targets and to ensure scale up is occurring adequately in all vulnerable populations. Such data will allow for monitoring success of individual programs and allow near "real-time" course correction.

How Much Would a National PrEP Program Cost?

In today's time of budgetary restraints, we recognize the necessity of providing solutions that are not only epidemiologically efficacious, but also practical financially. As detailed below, if the government uses its existing statutory authority to allow Americans access to international generics, a comprehensive national PrEP program ensuring free universal access to TDF/FTC, clinical care, and robust programming to mitigate barriers not directly related to price, would cost under $2 billion annually. Given that this is less than a tenth of the amount that the Federal Government already spends on domestic HIV care, we believe this to be a more than reasonable amount to spend on preventive measures which will almost assuredly be cost-saving in the near term. [85]

[84] Walters SM et al., "Awareness of pre-exposure prophylaxis (PrEP) among women who inject drugs in NYC: the importance of networks and syringe exchange programs for HIV prevention" *Harm Reduct J.* 2017; 14: 40.
[85] Kaiser Family Foundation. "U.S. Federal Funding for HIV/AIDS: Trends Over Time" (November, 2017) http://files.kff.org/attachment/Fact-Sheet-US-Federal-Funding-for-HIVAIDS-Trends-Over-Time

Clinical and Drug Costs of a National PrEP Program

Estimated annual cost of TDF/FTC and ongoing clinical care (per person) using Medicare Fee Schedules[86] and CDC PrEP Clinical Guidelines[87]

Description	*Cost (USD)*	*Units per Year*	*Annual Cost (USD) per person*
30-Day Supply TDF/FTC	$9.70 ($5.70 drug cost[88] + $4 distribution cost)	12	$116.40
4th Generation HIV Test (CPT 87389)	$29.38	4	$117.52
Renal Function Test (CPT 80069)	$10.72	2	$21.44
STI Tests (RPR, 3-site testing for GC NAAT) (CPT 86593, 87491, 87591)	$259.80	2	$519.66
Pregnancy Tests (CPT 81025)	$8.61	4	$4.79[89]
Physician Visit Cost (CPT 99214)	$111.95	4	$447.80
TOTAL COST			**$1,227.61**

Our point estimate of approximately $1,000 in non-drug related clinical cost is consistent with previously published estimates.[90] [91]

[86] Medicare Clinical Lab Fee Schedule and Medicare Physician Fee Schedule.
[87] US Public Health Service. Prerexposure Prophylaxis for the Prevention of HIV Infection int he United States - 2017 Update https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf
[88] Hill AM, Pozniak AL. "How can we achieve universal access to low-cost treatment for HIV?" *Journal of Virus Eradication*. 2016;2(4):193-197
[89] Accounts for women being 38% of those with PrEP indications
[90] Jussola JL et al., "The Cost-Effectiveness of Preexposure Prophylaxis for HIV Prevention in Men Who Have Sex with Men in the United States" *Ann Intern Med*. 2012 Apr 17; 156(8): 541–550.
[91] McKenney, J et al., "Optimal costs of HIV pre-exposure prophylaxis for men who have sex with men." *PLoS One*. 2017 Jun 1;12(6):e0178170.

Thus, if Americans can access low cost generics at a price comparable to what is available on the international market, the total cost of a year of PrEP clinical care is less than the average price of a 30-day supply of Truvada at current prices.

We next aim to explore the total cost of providing free clinical care, as well as drugs, in a national PrEP program. As previously discussed, the CDC estimates that 1.2 million Americans have indications for PrEP use. While it is unlikely that either all Americans who the CDC thinks need PrEP will actually use it or will need non-insurance based support to access it for PrEP care, we conservatively use this as an upper bound for estimation of the total annual price of such a program.

Number of PrEP Users	Percent of CDC Estimate	Cost of PrEP Clinical Care With Generic (US $)
120,000	10%	$147,313,200
240,000	20%	$294,626,400
360,000	30%	$441,939,600
480,000	40%	$589,252,800
600,000	50%	$736,566,000
720,000	60%	$883,879,200
840,000	70%	$1,031,192,400
960,000	80%	$1,178,505,600
1,080,000	90%	$1,325,818,880
1,200,000	100%	$1,473,132,000

Thus, the total annual cost of paying for *all* 1.2 million Americans with PrEP indications, inclusive of clinical and drug costs, assuming no coverage from *any* insurance program would be $1.473 billion. We note that this is significantly less than Gilead's domestic current revenue on Truvada alone, including for HIV treatment and other uses. We view

this as a framing tool to price a national PrEP access program, given that our healthcare system is already spending *in excess* of this to provide Truvada for PrEP and related clinical care to only ten percent of those who need it. **We believe the $527 million dollars in remaining existing spending should be used to mitigate barriers to PrEP access that are not directly related to cost.** Grants should be made to local public health services and community based organizations to develop and implement programs to overcome these barriers given their expertise and deep on the ground knowledge.

To frame a sense of the scale that such programs could entail on a national level, we present some ideas below as thought experiment:

- **Providing non-emergency medical transportation for routine clinical visits**
  One of the largest causes of PrEP discontinuation in vulnerable populations is the inability to access adequate transportation to get healthcare provider visits. Provisioning of free Non-Emergency Medical Transportation (NEMT) is well established to help mitigate these challenges. We assume that 10% of PrEP patients (120,000) will require fully subsidized transportation to healthcare providers -- four round trip trips per year at an average cost of $40 per trip.[92]
  Potential Budget: $20 Million

- **Outreach, training and support to primary care physicians**
  Lack of physician awareness of PrEP or unwillingness to prescribe is a barrier to PrEP access. Development and implementation of educational programs for primary care providers is essential to increase the PrEP provider pool, especially in underserved areas. Especially important will be programs that assist providers in identifying appropriate patients as well as programs to improve medication adherence. [93]
  Potential Budget: $50 Million

- **Dramatically increasing awareness of PrEP among vulnerable populations**

[92] National Academies of Sciences, Engineering, and Medicine; Transportation Research Board. "Cost Benefit Analysis of Providing Non-Emergency Medical Transportation." https://www.nap.edu/read/23285/chapter/1
[93] Silapaswan A et al. Pre-Exposure Prophylaxis: A Narrative Review of Provider Behavior and Interventions to Increase PrEP Implementation in Primary Care. J Gen Intern Med. 2017 Feb;32(2):192-198.

As detailed above, vulnerable populations are often not aware of the existence, efficacy, and safety of PrEP. One solution to improve awareness is to fund a nationwide campaign engaging communities with information regarding PrEP. We used the cost of the successful anti-tobacco campaigns as an economic model.[94]
Potential Budget: $50 Million

- **Increase funding for organizations that directly engage with impacted communities, in order to increase capacity for patient centered advocacy, as well as national engagement with PrEP priorities.**

  We believe that organization who are closest to the impacted communities do the best job at serving those communities. Since the beginning of the AIDS epidemic, activism from community based organizations has played an invaluable role in fighting this plague. We are going to need to greatly increase capacity of our community based organizations (CBOs) in order to ensure that all populations are adequately being served by this program.
  Potential Budget: $250 Million

Even if these programs were fully funded, $120 million would remain for other opportunities. The purpose of enumerating these programs is not to suggest they are the correct ones, but to highlight the breadth and scale of potential programs that could be funded with very low cost TDF/FTC.

[94] Creamer, M. Anti-Smoking Campaigns Work, So Don't Quit Now. AdAge. Jan 2012. http://adage.com/article/news/funding-anti-tobacco-ads-fell-quitting-rate/232111/

Government Paths to Access Generic PrEP

There are two major pathways to generic PrEP in the United States:

March-In Rights

In 1980, the US Congress passed the Bayh-Dole Act to address concerns about the lack of commercialization of scientific advances made using public funds. Indeed, as the NIH has stated in their response to previous march-in petitions, the stated policy and objective of the Bayh-Dole Act is:

It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area.

By allowing universities and businesses that perform research to patent technologies developed using government funds, a wealth of treatments and technologies have been brought to the marketplace to great economic and health benefit of the American people. It does not escape us that a great number of treatments, including AZT as well as the compound at issue here, FTC, were commercialized under this program to much benefit to people living with HIV/AIDS. HIV remains a chronic, treatable disease in significant measure due to the success of this law and we believe a competitive and open marketplace for such drugs continues to drive innovation and incremental benefits for those in our community.

However, with respect to the implementation of PrEP throughout the US, such success cannot be claimed. That less than 10% of those with PrEP indications have prescriptions for PrEP is a gross failure and demonstrates, as dictated by statue 203(1)(a)(2), a “health or safety need” that is not being addressed. While some may note that Gilead has taken effort with its assistance plans and grants to nonprofit organizations to address this need, we do

not believe such efforts have been "reasonably satisfied" by such programs. Now, certainly it is not the duty of Gilead to eliminate HIV from the United States. However, the statute states that the government may invoke march-in rights when "action is necessary to alleviate health or safety needs". We believe we have demonstrated that a health or safety need exists, and it should be noted that the health and safety need is one of a pandemic, infectious agent, and therefore we believe that action is indeed necessary.

Whether or not one agrees with the previous findings by the NIH that it is not within their scope to control prices of drugs and technologies developed with public funds, one *could* ask the NIH to exercise their march-in rights not to reduce price directly, but rather to issue licenses to a number of other drug manufacturers to increase the supply and availability of TDF/FTC for PrEP.

Additionally we would like to highlight that the Bayh-Dole Act states as part of its "policy and objective" that one of the purposes of the legislation is to "***ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government.***" We believe that the argument we have made for march-in rights indeed ensures that the government utilizes its rights to meet the needs of the Government, while holding true to the other intentions of the law.

Additionally, with respect to our argument for march-in rights vis-a-vis previous denied petitions, we would like to note the statement of Senator Birch Bayh to the National Institute of Health on May 25, 2004 during the NIH Public Meeting on Norvir/Ritonavir March-in Request:

> "I empathize with the countless individuals in the U.S. and around the world who are suffering from AIDS. If it can be shown that the health and safety of our citizens is threatened by practices of a government contractor, then Bayh-Dole permits march-in rights, not to set prices, but to ensure competition and to meet the needs of our citizens. However, such a procedure must be supported by hard evidence that the need exists."

We believe that the actions of Gilead, do indeed "threaten….the health and safety of our citizens." Taking the Senator's words directly, we reiterate, once again, that a march-in

petition does not have to focus on price-fixing. Rather it is, as the Senator states, about the health and safety of our citizens, and the government's current inability to meet their needs. We believe that in the preceding pages we have demonstrated "by hard evidence" that such "need exists."

"Paid-Up License" Under 35 U.S.C. § 202(c)(4)

We believe we have made a compelling argument for the invoking of march-in rights which is unique to the previous unsuccessful petitions. While we have addressed many of the previous concerns around price cited in the NIH's response to such petitions, we have concern that the NIH might choose not to invoke march-in rights due to the narrow scope with which march-in rights were enacted under the federal statute. Therefore, we will highlight additional powers the NIH and other federal agencies have at their disposal to to alleviate the urgent public health concern at hand.

Separate from March-In rights, the Bayh-Dole Act grants the U.S. government the following rights on technologies developed using public funds:

> *"With respect to any invention in which the contractor elects rights, the Federal agency shall have a nonexclusive, nontransferrable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world."*

We could also petition the NIH to exercise its rights under 35 U.S.C. § 202(c)(4). By exercising its "paid-up license to practice or have practiced for or on behalf of the United States", the government may ask generic manufacturers to produce TDF/FTC on its behalf for use in a nationwide public health program to implement high rates of PrEP use for those with indications. The government, through the CDC, routinely contracts with manufacturers under comparable public health campaigns such as those for routine vaccinations, including the Vaccines for Children (VFC) program. Indeed the CDC states:

> *The Vaccines For Children (VFC) program is a federally funded program that provides vaccines at no cost to children who might not otherwise be vaccinated because of inability to pay. CDC buys vaccines at a discount and distributes them to grantees—i.e., state health departments and certain local and territorial public health agencies—which*

> *in turn distribute them at no charge to those private physicians' offices and public health clinics registered as VFC providers.*

We will ask that the NIH work with the CDC to use its "paid-up license" to allow similar contracts with generic manufacturers to manufacture TDF/FTC for similar programs. While some might argue that this is an unnecessarily drastic step, we believe PrEP implementation rates that are an order of magnitude lower than voluntary vaccination rates six years into FDA-approval is a public health failure and does indeed call for such drastic action.

"Use without License" Under 28 U.S.C. § 1498(a)

The federal government as well as any of its agencies (NIH, CDC) or assigned contractors have the power to infringe on any U.S. patent without permission of the patent holder under 28 U.S.C. § 1498(a). Indeed 28 U.S.C. § 1498(a) states:

> Whenever an invention described in and covered by a patent of the United States is used or manufactured by or for the United States without license of the owner thereof or lawful right to use or manufacture the same, the owner's remedy shall be by action against the United States in the United States Court of Federal Claims for the recovery of his reasonable and entire compensation for such use and manufacture.

Therefore, the NIH, CDC, or other federal agency has the immediate ability to contract with generic manufacturers of TDF/FTC for public health use onto the marketplace to generic competition today. The scope of 28 U.S.C. § 1498(a) is meant to be an "expeditious statutory regime for dealing with public health emergencies" and indeed "there is no injunctive remedy against such activities." [95] Thus, unlike March-In rights, the government does not need to justify its activities under the narrow scope of Bayh-Dole and could contract with generic manufacturers immediately. Such generic manufacturers would be protected from suit by Gilead as the broad reach of 28 U.S.C. § 1498(a) states that companies may only seek remedy by action against the U.S. government itself in the U.S.

[95] https://www.law.uh.edu/healthlaw/perspectives/Food/011207Current.html

Court of Federal Claims and not its contractors.[96] Gilead would then seek "reasonable and entire compensation for such use and manufacture" based on existing case law.[97]

Unlike March-In Rights, the US government routinely utilizes its power under 28 U.S.C. § 1498(a). In fact, it utilizes it so frequently that there is an entire case law behind it. We believe that 28 U.S.C. § 1498(a) provides an appropriate mechanism for the CDC to address the public health crisis at hand.

Conclusion

After decades of research, most of it publicly funded, we have the tools to eliminate HIV transmission. The racial, social, and geographic disparities in new HIV cases is unacceptable. The current low rate of PrEP utilization is one of the greatest public health implementation failures in the history of this country. The US Government should enforce its rights and make PrEP widely available at no cost to all Americans with indications in order to end the HIV epidemic. A National PrEP Program is essential to scaling-up PrEP use and addressing barriers not related to costs.

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PrEP4All is a NYC-based grassroots group of activists dedicated to increasing access to PrEP as an essential component of the biomedical model for HIV prevention. Please visit us at breakthepatent.org for more information.

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[96] https://www.wileyrein.com/newsroom-articles-3780.html
[97] https://www.uscfc.uscourts.gov/node/2927