No. 2024-2069

United States Court of Appeals For the Federal Circuit

THE UNITED STATES OF AMERICA,

Plaintiff-Appellant,

v.

GILEAD SCIENCES, INC. and GILEAD SCIENCES IRELAND UC,

Defendants-Appellees.

Appeal from the United States District Court for the District of Delaware, Case No. 1:19-CV-2103, Judge Maryellen Noreika

BRIEF OF *AMICI CURIAE* PrEP4ALL, AIDS ACTION BALTIMORE, amfAR, AVAC, HOUSING WORKS, AND TREATMENT ACTION GROUP IN SUPPORT OF APELLANT AND REVERSAL

Laurel Boman
Natalie Lesser
Joseph E. Samuel, Jr.
BERGER MONTAGUE PC
1818 Market Street, Suite 3600
Philadelphia, PA 19103
(215) 875-3000
lboman@bm.net

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Counsel for Amici Curiae

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2024-2069

Short Case Caption US v. Gilead Sciences, Inc.

Filing Party/Entity Amici Curiae listed in Section 1

Instructions:

1. Complete each section of the form and select none or N/A if appropriate.
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Date: December 19, 2024 Signature: */s/ Laurel Boman*

Name: Laurel Boman

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☑ None/Not Applicable
PrEP4All, Inc.		
AIDS Action Baltimore, Inc.		
The Foundation for AIDS Research		
AIDS Vaccine Advocacy Coalition		
Housing Works, Inc.		
Treatment Action Group		

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

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5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☐ **Yes (file separate notice; see below)** ☐ **No** ☑ **N/A (amicus/movant)**

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6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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STATEMENT OF IDENTITY AND INTEREST OF AMICI CURIAE

Amici Curiae PrEP4All, Inc., AIDS Action Baltimore, Inc., The Foundation for AIDS Research ("amfAR"), AIDS Vaccine Advocacy Coalition ("AVAC"), Housing Works, Inc., and Treatment Action Group ("TAG") (together, "Amici") are non-profit organizations that advocate for equitable access to Pre-Exposure Prophylaxis ("PrEP") medication. Their missions include working toward the elimination of HIV and AIDS, such as by promoting scientific research and innovation in HIV and AIDS prevention, providing or advocating for increased access to HIV testing and/or PrEP medications, speaking out on behalf of the often-marginalized people and communities affected by HIV and AIDS, advocating for a National PrEP Program[1] to cover the costs of PrEP medications for the uninsured, and working with policymakers to support and advance these goals.

Amici closely monitored the development of HIV prevention and PrEP and are uniquely positioned to explain the state of the art at the time of the government's invention and how PrEP's surprising success in preventing HIV transmission has provided an effective tool that could be used to finally end the HIV epidemic once and for all. Amici have an interest in the outcome of this litigation because Amici support the U.S. government's work on HIV/AIDS treatment and research goals,

[1] PrEP4All, *National HIV Prevention*, https://prep4all.org/national-hiv-prevention/.

view the CDC as the true inventor of PrEP, and seek to have Gilead held accountable for its unauthorized use of the CDC's breakthrough invention.

IDENTIFICATION UNDER RULE 29(a)(4)(E)(i)-(iii)

Pursuant to Federal Rule of Appellate Procedure 29(a)(4)(E), Amici state that (i) no party or party's counsel authored this brief in whole or in part; (ii) no party or party's counsel contributed money that was intended to fund preparing or submitting this brief; and (iii) no person other than Amici, its members, or its counsel, contributed money that was intended to fund preparing or submitting this brief.

STATEMENT REGARDING LEAVE TO FILE AMICUS BRIEF

The parties have consented to the filing of this amicus brief, in email correspondence dated November 13, 2024, with counsel for Plaintiff-Appellant the United States, Walter W. Brown of the U.S. Department of Justice, and in email correspondence dated November 14, 2024, with counsel for Defendants-Appellees Gilead Sciences, Inc. and Gilead Sciences Ireland UC, Mark C. Fleming of WilmerHale.

INTRODUCTION

Soon after HIV was identified as the cause of AIDS in 1984, some public health officials predicted that a vaccine could be ready for testing within a few years. Four decades later, despite significant advances in HIV treatment, a safe and effective vaccine remains elusive. Prior to PrEP, prevention efforts largely centered around behavioral modifications and occupational post-exposure prophylaxis, which reduced the rates of transmission but overall failed to stem the tide of new HIV transmissions. Against this historical backdrop, the efficacy of using a combination of the antiretroviral medications emtricitabine + tenofovir for PrEP emerged as a surprising forerunner in HIV prevention.

This brief summarizes the history and context leading to the development of emtricitabine + tenofovir PrEP therapy, a preventive that was invented by the government, whose clinical trials were paid for by the government and private charities, and whose popularity was created through the advocacy of activists, while Gilead has reaped billions on the back of those efforts. As Amici establish below, this history and context are powerful objective evidence of secondary considerations of the nonobviousness of the government's patent claims. They provide "an important check against hindsight bias" reflected in the jury's verdict and the district court's failure to grant judgment as a matter of law. *Bristol-Meyers Squibb Co. v. Teva Pharma. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Amici and their

members were among those activists who closely followed this history as it was made, pressing for funding, tracking the numerous advances and setbacks, and advocating for widespread use of PrEP, because Amici view PrEP as an essential tool to end the AIDS epidemic once and for all.

ARGUMENT

I. The HIV Epidemic: Decades of Devastation and Disappointment

A. History of the Epidemic

The emergence of HIV/AIDS in the early 1980s sparked one of the most significant public health crises in recent history. In 1981, medical researchers first reported cases in homosexual men in New York and California developing rare and deadly cases of pneumonia and cancer due to a condition that dramatically weakened their immune systems.[2] Within a year, the Centers for Disease Control & Prevention ("CDC") reported that the poorly understood disease had already reached "epidemic proportions."[3] By the end of the decade, the epidemic had already claimed almost 90,000 lives in the United States alone—a number that would tragically grow to over 362,000 by the end of the 1990s, at one point becoming the leading cause of death for 25-to-44-year-olds.[4]

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[2] amfAR, *Snapshots of an Epidemic: An HIV/AIDS Timeline*, https://www.amfar.org/about-hiv-aids/snapshots-of-an-epidemic-hiv-aids/.
[3] Lawrence K. Altman, *New Homosexual Disorder Worries Health Officials*, N.Y. Times, May 11, 1982.
[4] amfAR, *supra* note 2.

Early in the epidemic, HIV/AIDS was poorly understood and impervious to treatment, contributing to public anxiety and social discrimination against people with AIDS.[5] HIV—the virus that causes AIDS—was not isolated until 1984.[6] While there were early hopes that the isolation of HIV would lead to the rapid development and deployment of a vaccine, treatment, and prevention, all remained elusive through the 1980s: as Dr. Meg Doherty, Director of the World Health Organization (WHO) Global HIV, Hepatitis, and Sexually Transmitted Infections Programs, explains, "[w]ith no effective treatment available in the 1980s, there was little hope for those diagnosed with HIV, facing debilitating illness, social isolation and sadly, in most cases, certain death within years."[7]

B. Unmet Need for Prevention

The 1990s saw breakthroughs in the *treatment* of HIV/AIDS—including the announcement in 1996 of the success of "highly active antiretroviral treatment" (HAART), a three-drug cocktail that significantly reduced AIDS-related mortality[8]—but *prevention* efforts still lagged.[9] Throughout the 1980s and 1990s, community and public health efforts focused primarily on behavioral interventions.

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[5] *Id.*
[6] *Id.*
[7] World Health Organization, *Why the HIV Epidemic is Not Over*, https://www.who.int/news-room/spotlight/why-the-hiv-epidemic-is-not-over.
[8] Health Resources & Services Administration, *1995: First Protease Inhbiitor Becomes Available*, https://ryanwhite.hrsa.gov/livinghistory/1995.
[9] World Health Organization, *supra* note 7.

"Safer sex" strategies were used as a concerted public health measure,[10] including emphasis on condom use and risk-reduction counseling.[11] For intravenous drug users at risk of HIV, clean needle exchange programs were developed as a first-line intervention.[12] However, while behavioral interventions delivered "substantial reductions in HIV incidence in some populations," this approach had inherent limitations, and was unable bring about an end to the epidemic.[13]

By the 2000s, scientific and public health communities began to focus more intently on biomedical interventions—tools that would prevent infection at the biological level rather than relying solely on changes in behavior. Throughout this 2000s time period, approximately $1 billion a year was spent researching technologies to prevent HIV transmission.[14] Hundreds of millions of dollars in HIV

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[10] Ronald Bayer & Gerald M. Oppenheimer, *Joseph Sonnabend and the AIDS Epidemic: Pioneering and Its Discontents*, 111 Am. J. Public Health 1243, 1243 (2021).

[11] Appx32367.

[12] Appx32646.

[13] Albert Y. Liu, Robert M. Grant & Susan P. Buchbinder, *Preexposure Prophylaxis for HIV Unproven Promise and Potential Pitfalls*, 296 JAMA 863, 863 (2006); *see also* Columbia Mailman School of Public Health, *Counseling at the Time of HIV Testing Does Not Result in Reduced STIs* (Oct. 22, 2013) https://www.publichealth.columbia.edu/news/counseling-time-hiv-testing-does-not-result-reduced-stis (discussing limitations of risk-prevention counseling approach).

[14] HIV Vaccines and Microbicides Resource Tracking Working Group, Capitalizing on Scientific Progress: Investment in HIV Prevention R&D in 2010 at 34 (July 2011) https://avac.org/resource/report/capitalizing-on-scientific-progress-investment-in-hiv-prevention-rd-in-2010/; AVAC, *Global HIV Prevention R&D Investment by*

prevention research funding was poured into HIV vaccine research.[15] Unfortunately, these efforts initially did not yield a successful pre-exposure prophylactic solution.

During this period, guidelines were developed for post-exposure prophylaxis (PEP). PEP sought to use HIV antiretroviral drugs to prevent HIV in individuals *after* the individuals had been exposed to HIV, but the efficacy of PEP remained in doubt. The Centers for Disease Control and Prevention's (CDC) September 2005 guidelines listed multiple PEP regimens, though one of the guideline's authors, Dr. Walid Heneine, testified at trial that these recommendations should be taken "with a grain of salt" due to the absence of direct evidence of efficacy.[16] Additionally, as Dr. Robert Grant testified at trial, the toxic profile of drugs used for PEP made them unsuitable for pre-exposure prophylaxis (PrEP) for people without HIV to take over prolonged periods to prevent HIV transmission.[17] Notably, the Food and Drug Administration (FDA) has never approved a drug regimen specifically for PEP.[18] As a result, despite some incremental progress in treatment and prevention, the early 2000s remained a time of pressing unmet need for reliable, evidence-based

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Technology Category, 2000-2016 (July 20, 2017), https://avac.org/resource/infographic/global-hiv-prevention-rd-investment-by-technology-category-2000-2016/.

[15] AVAC, *Global HIV Prevention R&D Investment by Technology Category, 2000-2016* (July 20, 2017), https://avac.org/resource/infographic/global-hiv-prevention-rd-investment-by-technology-category-2000-2016/.

[16] Appx32308.

[17] Appx32383.

[18] Appx32369.

biomedical HIV prevention methods that could complement existing behavioral strategies and treatment breakthroughs.

At the beginning of the epidemic, many believed a "vaccine would be easily developed and rapidly deployed."[19] This was based on the widespread prior success in developing vaccines for a wide range of viral diseases. However, developing protective immunity after natural infection did not occur in the case of HIV.[20] The first wave of HIV vaccine research, starting in 1986, focused on neutralizing antibodies as an effect to protect against HIV transmission akin to a vaccine developed against hepatitis B.[21] This effort ended in 2003 when efficacy trials held in Thailand and North America reported negative results.[22] The next wave of research, starting in 1995, focused on the development of recombinant viral vectors, or genetically modified live viruses, to create immunity.[23] Unfortunately, vaccines developed under this theory also had unsuccessful results.[24]

By 2000, renewed efforts were being made to support and fund vaccine research. As the Treatment Action Group ("TAG") recognized, "[w]ith the staggering numbers of HIV infections around the globe and the prohibitive cost and

[19] José Esparza, *What Has 30 Years of HIV Vaccine Research Taught Us?*, 2013 Vaccines 513, 513 (2013).
[20] *Id*.
[21] *Id.* at 516-17.
[22] *Id.* at 517.
[23] *Id.* at 517-18.
[24] *Id.* at 518.

limited effectiveness of current antiretroviral therapy, the only way to stem the tide of the epidemic will be to develop a safe and effective vaccine to protect the uninfected from HIV transmission."[25] Despite persistent disagreements regarding appropriate funding and the best entity to pursue research, there was continued support for pursuing vaccine research.[26]

The AIDS Vaccine Advocacy Coalition ("AVAC") reported in 2002 that "HIV continues to spread at the alarming rate of nearly 14,000 new cases each day, public health experts still believe that preventative AIDS vaccines are urgently needed."[27] But AVAC also acknowledged that there were many unanswered questions, including "what immune response a vaccine needs to elicit to prevent HIV disease" and that significant funding and support was needed.[28] Specifically, this required hundreds of millions of dollars in funding and tens of thousands of volunteers to participate in vaccine trials.[29] There was a "wealth of vaccine

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[25] Gregg Gonsalves, *Statement on the Vaccines for a New Millenium Act of 2000*, Treatment Action Group, https://www.treatmentactiongroup.org/statement/statement-on-the-vaccines-for-the-new-millennium-act-of-2000/.

[26] *Id.*

[27] AVAC, *V Years & Counting: Science Urgency and Courage* 5 (2002), https://avac.org/resource/report/2002-avac-report-5-years-and-counting-science-urgency-and-courage/.

[28] *Id.* at 2.

[29] *Id.*

candidates in the pipeline for early phase testing" but some reluctance in the public and private sectors to support continued clinical trials.[30]

During this time, there was progress in vaccine and prophylactic protection research, but it had not advanced enough to be considered truly effective or promising. Several vaccines were in the pipeline, including a vaccine by Merck slated for a Phase III study in 2004[31] and an "experimental HIV vaccine" from the Vaccine Research Center that was "in line right behind Merck."[32] The CDC also prepared for the potential implementation of HIV vaccines.[33] Yet, despite tempered optimism, that same year AVAC admitted that just "five years away from the date former President Bill Clinton set as a goal for finding the AIDS vaccine, no one knows if any of the current experimental vaccines will work."[34]

As an alternative to a vaccine, there was some funding and research devoted to microbicides. "A microbicide is a cream, gel, or other formulation . . . to prevent HIV/AIDS and other sexually-transmitted diseases through topical application to genital surfaces."[35] Microbicides, as an alternative to a vaccine, were explored as a means to provide a wider range of options in HIV prevention. Prior to 2006, vaginal

[30] *Id.* at 9.
[31] *Id*. at 2, 9-10.
[32] *Id*. at 13.
[33] *Id.* at 36.
[34] *Id.* at 2.
[35] *Id.* at 20.

microbicide gels were a promising HIV prevention technology, but they had not yet been shown to be effective.

As a result of these unsuccessful efforts, there continued to be a huge unmet need. Dr. Heneine testified at trial that in 2004, HIV prevention "was not [in] a good state. Worldwide we were getting about 2.5 million new infections, the U.S. as well, we were getting a lot of infections. There was no vaccine available. . . . So really there was an urgency to find a biomedical intervention that would protect people."[36] In 2005, Dr. Thomas Coates concurred, noting "[i]n 1985 … people predicted that a vaccine and an end to AIDS were at hand" but now we are "20 years and 60 million infections later" and it is clear "there's still a long road ahead."[37]

HIV treatment alone was insufficient, and there was a desperate need for prevention.[38] By 2005, the extent of benefits from education and messaging regarding behavioral change had been reached. Yet, new transmissions were ongoing. Dr. Stephen Smith agreed, stating that "there is no question of the need for interventional strategies to stem the overwhelming tide of new infections."[39] Similarly, in 2005, AVAC noted that "[a] lot of people, rich and poor, are going to

[36] Appx32253.
[37] Appx35540.
[38] Joan Stephenson, *New HIV Prevention Strategies Urged*, 292 JAMA 1163 (2004).
[39] Stephen M. Smith, *Pre-exposure Chemoprophylaxis for HIV: It is Time*, 1 Retrovirology 1, 1 (2004).

want to increase their defenses against HIV infection."[40] By August 2006, "[t]here [was] an urgent need to expedite the assessment of new and readily available biomedical approaches to the prevention of HIV infection" since there was a "current lack of an effective biomedical intervention."[41]

Discussing the period from 2004 to 2006, Dr. Grant conceded that "we really had nothing" to prevent a person from contracting HIV:

> A colleague of mine had said after one of the HIV vaccine trials failed, he said we're really groping in the dark, that was the state of the science of biomedical prevention, biomedical intervention, we had good success with condoms and counseling in the 1980's, but by the year 2004, people were getting tired of condoms and abstaining from sex, they wanted to get back to their lives. And so we really didn't have anything. A friend of mine did a published review of randomized rigorous clinical trials of HIV prevention, 27 had been completed as of 2003. None of them showed a significant benefit over just making condoms available and counseling.[42]

As a result, there was considerable "frustration in the field about how vaccines were not working, none of the candidates . . . were being successful."[43]

"Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would not have persisted had the solution been obvious." *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d

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[40] AVAC, Will a Pill a Day Prevent HIV: Anticipating the Results of the Tenofovir PrEP Trials at 7 (Mar. 1, 2004), https://avac.org/resource/will-a-pill-a-day-prevent-hiv-anticipating-the-results-of-the-tenofovir-prep-trials/.
[41] Appx03833, Appx03839.
[42] Appx32367-Appx32368.
[43] Appx32382.

928, 936 (Fed. Cir. 2019) (quoting *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016)). In 2005, there were approximately 4.9 million new HIV transmissions, and in total, there were over 40 million people in the world living with HIV.[44] In the United States alone, there were approximately 35,500 reported new HIV transmissions.[45] Transmission rates remained high and there was nothing to stem the tide. As of February 2006, there was an urgent unmet need and the road to prevention was littered with failures.

II. The Continued Search for Effective Prevention: The Beginnings of Tenofovir-Based PrEP

By 2005, AVAC acknowledged that "other new prevention technologies are likely to arrive sooner than a vaccine"[46] and highlighted current research "that could change the way we think about preventing HIV infection[:]" tenofovir for PrEP.[47] Around that time, tenofovir was the "only . . . candidate being evaluated as PrEP."[48]

[44] UNAIDS & World Health Organization, AIDS Epidemic Update 1 (2005), https://data.unaids.org/publications/irc-pub06/epi_update2005_en.pdf.
[45] Department of Health and Human Services, HIV Surveillance Report 35 (2005), https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2005-vol-17.pdf.
[46] AVAC, *supra* note 40 at 8.
[47] *Id.* at 1.
[48] *Id.* at 27. *See also* Appx32254 ("There was only one drug that was under serious consideration for PrEP [around 2004] and that drug was called Tenofovir.").

Tenofovir for PrEP had proven promising in a 1995 study (the "Tsai study" or "Tsai 1995") published in the Journal of Science.[49] In this study, researchers injected tenofovir 48 hours before monkeys were exposed to a large viral load of simian immunodeficiency virus ("SIV").[50] The results were encouraging: tenofovir prevented transmission of SIV in all treated monkeys.[51] However, the study had serious limitations. The dose of tenofovir was several times higher than the average approved dose for human use,[52] and the virus, the host, and the circumstances of exposure were all different.[53]

Gilead was skeptical and declined to pursue an injectable form of tenofovir for PrEP.[54] Indeed, subsequent studies gave reason to be cautious. In one study, for

[49] Che-Chung Tsai et al., *Prevention of SIV Infection in Macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine*, 279 Science 1197 (1995).
[50] Appx03747; Appx34197-Appx34198. SIV is a virus similar to HIV but is expressed in monkeys. Appx32381-Appx32382.
[51] Appx03748; Appx34197-Appx34198.
[52] Appx34198.
[53] Appx34200-Appx34201 ("[A]nimal models may not be directly relevant to humans because of differences in the virus (cell-free SIV vs HIV-laden semen), differences in the host (new world monkeys vs humans), differences in the circumstances of exposure (atraumatic application of virus in resting animals vs sexual intercourse in humans), differences in the infectious does (>1 Monkey Infectious Dose vs <1 human infectious dose), and differences in adherence (100% in monkeys vs. <100% in humans)").
[54] *Gilead Sciences, Inc. v. United States*, No. IPR2019-01456 (P.T.A.B. Feb. 5, 2020), Ex. 1044 at 2.

instance, tenofovir "showed at best 50 percent reduction in viral transmission" and there were concerns about success at a large scale.[55]

Against this backdrop, AVAC explained in 2004 that while "[r]esearch in animals indicates that tenofovir, used as PREP, may be effective in reducing the risk of HIV transmission[, w]e should guard against over optimism: no one knows whether tenofovir will be appropriate for use as PREP."[56] Researchers agreed, explaining that PrEP "may prove to be ineffective in humans"[57] and that "[r]eliable information on the effectiveness and . . . safety of PrEP as an HIV prevention intervention will not be available until the studies currently being planned and implemented are completed and their data analyzed and reported."[58] While there were some reports around this time of off-label use of tenofovir-based products for PrEP, AVAC and researchers warned against it, because it was not yet shown to be effective.[59] As Dr. Coates noted, "[t]he only way to find out" if tenofovir can "delay

[55] Appx32387-Appx32388.
[56] AVAC, supra note 40, at 1.
[57] Appx34201.
[58] Appx03821.
[59] AVAC noted in 2005 that tenofovir "can already be prescribed 'off label' … no one knows if it can reduce HIV infection rates in HIV-negative people" and warned community members that taking tenofovir off-label as PrEP was "a bad idea" because it "is unknown whether they are getting any protection from the drug." AVAC, *supra* note 40 at 2, 5. Dr. Coates noted that while tenofovir-based PrEP was promising there was a lack of clinical efficacy data and that he "would never recommend a prevention strategy" like "tenofovir … without knowing for sure that it protects a person from HIV without harming them." Appx35540. Similarly, Dr.

or block infection … for HIV-negative people … is through a placebo-controlled trial,"[60] several of which were planned or underway by 2005.[61]

Notably, other than providing samples for these studies, Gilead did not substantially engage in efforts to further PrEP research. The clinical trials were all sponsored and funded by the U.S. government and/or nonprofits.[62] Gilead was so skeptical of PrEP that Science magazine reported in 2005 that "[i]n an unusual twist, tenofovir's maker . . . has no interest in pursuing PrEP because of fears that uninfected people who take tenofovir and still become infected might sue the company."[63]

Instead, the U.S. government led the way. Around the time that the tenofovir clinical trials were planned and/or ongoing, the CDC and NIH sponsored a meeting to evaluate the state of the art on PrEP research.[64] At this meeting, the results of a

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Grant and his co-authors noted that "we are concerned about possible off-label or unmonitored PrEP use in the community" because "[t]he currently available information is not sufficient to recommend PrEP use." Albert Y. Liu, Robert M. Grant & Susan P. Buchbinder, *Preexposure Prophylaxis for HIV Unproven Promise and Potential Pitfalls*, 296 JAMA 863, 863 (2006).

[60] Appx35540.

[61] *See* AVAC, *supra* note 40 at 4.

[62] Treatment Action Group, What's in the Pipeline, New HIV Drugs, Vaccines, Microbicides, HCV and TB Treatments in Clinical Trials at 27 (July 2005), https://www.treatmentactiongroup.org/wp-content/uploads/2011/10/2005-pipeline-full.pdf.

[63] *Gilead Sciences, Inc. v. United States*, No. IPR2019-01456 (P.T.A.B. Feb. 5, 2020), Ex. 1096 at 1004.

[64] Appx32256-Appx32257.

new study presented by CDC researchers cast serious doubts on the efficacy of tenofovir for PrEP. The study made several modifications to Tsai 1995 to more closely mimic human use of tenofovir for PrEP by using oral tenofovir rather than injected tenofovir at the "same dose that people would be getting,"[65] and used a "repeated-exposure model" that "attempt[ed] to approximate high-risk HIV infection in humans through multiple inoculations of macaques with levels of SHIV that are closer to the levels of HIV-1 noted in the semen of humans with acute infection," as opposed to a single, high-dose exposure,[66] and used SHIV, which is "SIV modified with some components of human HIV-1," rather than SIV.[67]

The results were disappointing.[68] Infection was merely "delayed,"[69] and the results were not statistically significant by week 14.[70] "All but one of the monkeys in the study were infected within 14 weeks."[71] When these results were presented at the CDC/NIH meeting, Dr. Heneine testified that "There was this kind of eerie silence. . . . I think the audience . . . expected a different result. They expected to see a very high level of protection, like what was previously described by the Tsai paper,

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[65] Appx32259-Appx32260.
[66] Appx03834.
[67] AVAC, *supra* note 40 at 3.
[68] Gus Cairns, *Pre-exposure Prophylaxis May Need Large Doses to Work* (Sept. 19, 2006), https://www.aidsmap.com/news/sep-2006/pre-exposure-prophylaxis-may-need-large-doses-work (last accessed Dec. 15, 2024).
[69] Appx32258.
[70] Appx03838.
[71] Cairns, *supra* note 68.

but unfortunately it was not the case."[72] AVAC noted that the data "highlight the fact that the protective effect of tenofovir, and the longevity of an effect if there is one, are far from established."[73]

Based on these disappointing results, the CDC inventors "decided to . . . figure out how we need to move the needle from partial to high protection."[74] The inventors explored "what drugs do we need to combine with TDF to boost . . . efficacy."[75] To do so, the inventors designed a study to "evaluate [licensed drugs] one by one, there were different classes, different activity, different profiles, they come in various properties" to "figure out which ones would make sense to combine."[76] The inventors ultimately settled on a multi drug study comparing tenofovir and emtricitabine (FTC), which was not "the obvious choice."[77]

At that point, FTC was an unknown. As of March 2005, there was no "preliminary data at all showing that FTC could be an acceptable PrEP agent" or even was "active as a preventative agent."[78] Dr. Grant testified that, around the 2004 to 2006 time frame, no one was thinking of using FTC for PrEP because FTC "had a very low barrier to drug resistance" and "there was great concern that FTC . . .

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[72] Appx32259.
[73] AVAC, *supra* note 40 at 3.
[74] Appx32260.
[75] Appx32261.
[76] *Id.*
[77] Appx32261-Appx32262.
[78] Appx32385.

would not be appropriate for intervention."[79] Accordingly, a "key goal" of the CDC inventors in designing their study was to evaluate FTC.[80]

The CDC inventors tested the tenofovir-FTC combination on an animal model that sought to more closely mimic human exposure to HIV.[81] The results "changed everything."[82]

III. From Proof of Concept to Proven Efficacy: Truvada PrEP Emerges as a Highly Effective Tool to End the HIV Epidemic

In the CDC study, all animals given the tenofovir-FTC combo were protected.[83] These results "clearly showed [a] proof of concept [to get to one] hundred percent" protection.[84]

The study results were accepted as a "late breaker"[85] at the 2006 Conference on Retroviruses and Opportunistic Infections ("CROI") and the data was "enthusiastically accepted," generating a lot of media coverage.[86] The results "infused a whole new era of enthusiasm and hope in the PrEP field."[87] Community

[79] Appx32373.
[80] Appx32264.
[81] *See* Appx32387; *see also* Appx32286-Appx32287 (describing the various "refinement[s] over other models").
[82] Appx32387.
[83] Appx32270.
[84] Appx32271.
[85] Appx32276 ("A late breaker is where you submit after the submission deadline" and is used for "really highly impactful data that you need to make public.").
[86] Appx32277.
[87] Appx32277.

activists "call[ed] for more studies to see how the concept might be applied to humans."[88] Because "[t]he history of AIDS research is teeming with claims that a cure, vaccine, microbicide, or other needed scientific advance is just around the corner" AVAC reported that "[i]t is possible that PrEP is just the latest false hope in an epidemic."[89] Well-designed clinical trials were essential to establish that the efficacy shown in monkey studies extended to various patient populations at risk of HIV.

A CDC study in Botswana and the iPrEx study swiftly changed course to mimic the tenofovir-FTC regimen, substituting tenofovir with Truvada, Gilead's tenofovir-FTC combination pill approved at the time only for treatment.[90] By 2008, several clinical trials had adopted the tenofovir-FTC regimen.[91]

These studies proved that a biomedical intervention could work in real patients around the world. iPrEx was the first study to issue results, and "proved for

[88] Gus Cairns, *CROI: Successful PREP Trial in Monkeys Sparks Call for more Research* (Feb. 7, 2006), https://www.aidsmap.com/news/feb-2006/croi-successful-prep-trial-monkeys-sparks-call-more-research/.
[89] AVAC, *Anticipating the Results of PrEP Trials: A Powerful New HIV Prevention Tool May Be On the Horizon. Are We Prepared?*, at 4 (Aug. 2008), https://avac.org/resource/report/anticipating-the-results-of-prep-trials-a-powerful-new-hiv-prevention-tool-may-be-on-the-horizon-are-we-prepared/.
[90] Appx32285-Appx32286.
[91] *See* AVAC, supra note 89, at 7.

the first time that HIV prevention using PrEP would be possible."[92] iPrEx showed an overall efficacy of 44%,[93] but the data revealed that adherence was key. When taken as directed, Truvada PrEP was nearly 100% effective.[94] Shortly before the NIH investigators published results of the iPrEx trial, the NIH briefed the CDC on the data. The outstanding results were met with "[c]elebration, shock, [and] surprise" at the CDC,[95] since the efficacy that had been established by the CDC's animal studies was now also established in human patients. The public reaction was similar—"people were thrilled."[96] Time magazine hailed the iPrEx study as the top medical breakthrough of 2010.[97] Mitchell Warren, the executive director of AVAC, "called the study 'a great day for the fight against AIDS' and said gay men and others at risk needed to be consulted on the next steps."[98] These unexpected but superior

[92] HIV Vaccines and Microbicides Resource Tracking Working Group, Capitalizing on Scientific Progress: Investment in HIV Prevention R&D in 2010, at 6 (July 2011), https://avac.org/resource/report/capitalizing-on-scientific-progress-investment-in-hiv-prevention-rd-in-2010/.
[93] Appx04134.
[94] *See* Peter L. Anderson et al., *Emtricitabine-Tenofovir Exposure and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex With Men*, https://pmc.ncbi.nlm.nih.gov/articles/PMC3721979/.
[95] Appx32390.
[96] Appx32391.
[97] *See* Alice Park, *The Top 10 Medical Breakthroughs* (Dec. 9, 2010), https://web.archive.org/web/20111107084242/http://www.time.com/time/specials/packages/article/0,28804,2035319_2034529_2034513,00.html.
[98] Donald G. McNeil Jr., *Daily Pill Greatly Lowers AIDS Risk, Study Finds*, N.Y. Times (Nov. 23, 2010).

results demonstrate the non-obviousness of the government's patent claims. *See, e.g., Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015).

Gilead remained skeptical. The FDA met with Gilead in February 2009 to encourage Gilead to submit data from these clinical trials to support approval of Truvada for PrEP.[99] At the meeting, Gilead indicated that it did "not plan to pursue the PrEP indication or to promote [Truvada's] use for PrEP."[100] Gilead finally submitted an application for Truvada approval for PrEP in December 2011, relying on the iPrEx and Partners PrEP clinical trials.[101] Activists lauded the application, noting that "the approval of Truvada would represent a historic moment for the biomedical prevention field."[102]

[99] Appx32444, Appx 32449.
[100] Appx32447-Appx32448.
[101] Appx32453-Appx32454.
[102] Richard Jeffreys, *Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies* (July 2012), https://www.treatmentactiongroup.org/resources/pipeline-report/2012-pipeline-report/preventive-technologies-research-toward-a-cure-and-immune-based-and-gene-therapies/.

On July 16, 2012, the FDA approved Truvada for PrEP. The approval was hailed as a "watershed moment"[103] and "a historic advance for HIV prevention efforts."[104]

IV. PrEP Has Been a Resounding Success, Strengthening Hopes For an HIV-Free Future For Many.

The availability of a reliable, proactive means of preventing HIV transmission was a transformational tool of self-protection that allowed individuals to take active control of their own health. The reaction from commentators, public health experts, and the market was immensely positive.

A. The industry heaped remarkable praise on PrEP and its positive effects on individuals at risk of HIV transmission.

The reaction to PrEP was overwhelmingly positive, as it marked a paradigm shift in how the community would think about HIV prevention. Time Magazine hailed the combination treatment as a "potent" weapon against HIV/AIDS which "marks a big step toward controlling the spread of HIV and AIDS, not just in the

[103] AVAC, *AVAC Welcomes Landmark FDA Approval of (Truvada) TDF/FTC as PrEP for HIV – Urges Immediate Steps to Make Important New HIV Prevention Option Available for the Men and Women Who Need It*, https://avac.org/press-release/avac-welcomes-landmark-fda-approval-of-truvada-tdf-ftc-as-prep-for-hiv-urges-immediate-steps-to-make-important-new-hiv-prevention-option-available-for-the-men-and-women-who-need-it/.

[104] James Krellenstein & Jeremiah Johnson, *PrEP Pricing Problems*, https://www.treatmentactiongroup.org/resources/tagline/tagline-spring-2016/prep-pricing-problems.

U.S. but worldwide as well."[105] Similarly, the Boston Globe reported that the combined treatment of emtricitabine and tenofovir in Truvada for PrEP was "considered one of the most significant advances in the fight against AIDS" and was, indeed, "a total game-changer[.]"[106] The Washington Post recognized the "breakthrough research" leading to the approval of the combined treatment of emtricitabine and tenofovir disoproxil fumarate in Truvada for PrEP.[107] As researchers continued to investigate PrEP's efficacy even years after it had been disclosed and claimed in the Government's patents, PrEP was repeatedly hailed as a breakthrough. In 2015, Ariana Eunjung Cha of the Washington Post wrote, "As far as emotions go, AIDS researchers tend to be a staid bunch who look skeptically at every new finding. But the results of a study released this week on an HIV prevention drug have many cheering."[108]

Praise for PrEP and the advance it represented was widespread. The named inventors on the Government's patents were twice nominated for the premier CDC

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[105] *Gilead Sciences, Inc. v. United States*, No. IPR2019-01456 (P.T.A.B. Feb. 5, 2020), Ex. 2009 at 1-2.
[106] *Gilead Sciences, Inc. v. United States*, No. IPR2019-01456 (P.T.A.B. Feb. 5, 2020), Ex. 2010 at 2.
[107] *Gilead Sciences, Inc. v. United States*, No. IPR2019-01456 (P.T.A.B. Feb. 5, 2020), Ex. 2011 at 1.
[108] Ariana Eunjung Cha, *In New Study, 100 Percent of Participants Taking HIV Prevention Pill Truvada Remained Infection-Free*, The Washington Post, Sept. 4, 2015 (referencing a study conducted by Kaiser Permanente showing that 100% of more than 600 individuals on Truvada PrEP remained HIV-free over a period of 2.5 years).

award for excellence in science for their work as reflected in the patents.[109] Commentators stated in 2010 that a promising study meant the study's release date "will likely go down as a pivotal day in the history of the AIDS epidemic."[110] In 2015, others noted that "[t]he development and implementation of, and continuing research on, pre-exposure prophylaxis (PrEP) have brought us significantly closer to a watershed in efforts to end HIV as a global epidemic."[111] In 2019, the United States House Committee on Oversight and Reform lauded FDA approval of PrEP for its "remarkable scientific work" and labeled PrEP "the most efficacious [HIV] prevention intervention known."[112] The House Committee specifically recognized the "CDC scientists [who] discovered that adding a drug called FTC to tenofovir increased protection . . . it's the combination of those two medications which is FDA-approved today."[113]

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[109] *Gilead Sciences, Inc. v. United States*, No. IPR2019-01456 (P.T.A.B. Feb. 5, 2020), Ex. 2012 at 1; *Id.*, Ex. 2021 at 1.

[110] David Evans, *PrEP Works: The Little Blue Pill That Could* (Nov. 23, 2010), https://www.poz.com/article/hiv-prep-iprex-19471-5437 ("On this day, researchers published data . . . proving that daily use of the antiretroviral (ARV) drug Truvada (tenofovir and emtricitabine) by HIV negative people cuts new infections by at least 44 percent. That small blue tablet, which only needs to be taken once per day, is going to have a very big future in HIV prevention.")

[111] Tim Horn & Richard Jeffreys, *Preventive Technologies: Antiretroviral and Vaccine Development* (July 2015), https://www.treatmentactiongroup.org/resources/pipeline-report/2015-pipeline-report/preventive-technologies-antiretroviral-and-vaccine-development-3/.

[112] *Gilead Sciences, Inc. v. United States*, No. IPR2019-01456 (P.T.A.B. Feb. 5, 2020), Ex. 2013 at 7.

[113] *Id.* at 5; *see also id.* at 35.

This is incredibly strong indicia of industry praise because "[i]ndustry participants … are not likely to praise an obvious advance over the known art." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1334 (Fed. Cir. 2016); *see also Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) ("[I]ndustry praise ... provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected [the claimed invention]."). Importantly, praise for Gilead's release of products that practice the Government's invention is equally relevant to nonobviousness. *See WBIP*, 829 F.3d at 1334 ("Evidence that the industry praised a claimed invention *or a product which embodies the patent claims* weighs against an assertion that the same claim would have been obvious.") (emphasis added). It is especially compelling that praise continued to be heaped on the efficacy of PrEP for several years after it was disclosed in the Government's patents. There could hardly be a clearer example of hindsight bias than to hold a patent invalid for obviousness when the invention claimed therein was still being praised as a remarkable breakthrough from test results years after the patent issued.

B. PrEP has been a commercial home run—ironically, *despite* Gilead's noninvolvement in the development and initial promotion of Truvada for PrEP.

Despite Gilead's initial refusal to market Truvada PrEP, it has been immensely successful, thanks largely to government and community advocacy

efforts. Regrettably, despite the praise and excitement for Truvada PrEP, Gilead did very little to market the drug until activists and the government proved there was a market.

The year after the FDA approved Truvada for PrEP, Gilead did not view PrEP as a commercial opportunity, claiming that "the market wasn't really ready."[114] Initially, Gilead relied on promotion by the government,[115] or by the community, giving grants to community groups in amounts that paled compared to Gilead's advertising spending for the period.[116] Gilead was extremely slow to act on any form of commercialization following the 2012 breakthrough approval of PrEP and its marketing strategy did not change until "[l]ate 2015, early 2016."[117] In 2014, Gilead reported a mere $2.3 million for PrEP-related educational efforts—for "grants and support to community organizations, demonstration projects and research efforts that raise awareness about PrEP among at-risk populations."[118] In 2015, Gilead gave $11

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[114] Appx32821.
[115] *See* Appx33321 ("[T]he government was promoting [Truvada] use for PrEP").
[116] *Gilead Ups Stealth Marketing Campaign for PrEP, Skirting FDA Oversight*, AIDS Healthcare Foundation (Aug. 26, 2015) https://www.aidshealth.org/2015/08/gilead-ups-stealth-marketing-campaign-for-prep-skirting-fda-oversight/.
[117] Appx32822.
[118] *See* Gilead, Corporate Contributions Highlight Summary, at 3 https://www.gilead.com/~/media/files/pdfs/other/Highlights%20Brochure%20-%20FINAL.pdf (last accessed Dec. 19, 2024).

million in community grants[119] and told Bloomberg news that it "does not view PrEP as a commercial opportunity and is not conducting marketing activities around Truvada as PrEP[.]"[120]

Instead, activists and government officials educated the public on the use and efficacy of Truvada for PrEP. In 2014, over one hundred leading HIV/AIDS and health organizations voiced strong support for oral PrEP as an important HIV prevention strategy, in response to new CDC guidelines based on the FDA's approval of Truvada for PrEP.[121] In 2015, World Health Organization began recommending that people "at substantial risk of HIV infection should be offered tenofovir disoproxil fumarate (TDF)-based oral PrEP as an additional prevention

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[119] Gilead, Corporate Social Responsibility Report 2015 at 7, https://www.gilead.com/~/media/files/pdfs/other/h2_gil_csr_051116_final_web.pdf%20at%20pg%207 (last accessed Dec. 14, 2024). Gilead's spending on community grants appears to have peaked in 2015. In 2016 and 2017, Gilead gave approximately $7 million and $6 million in grants respectively. Gilead, Year in Review 2016 at 12, https://www.gilead.com/-/media/gileadcorpredesign/pdf/company/annual-esg-reports/fullreport_gilead_yir2016-(8).pdf; Gilead, 2017 Year in Review at 28 https://www.gilead.com/-/media/gileadcorpredesign/pdf/company/annual-esg-reports/final-year-in-review-426.pdf.

[120] *See Gilead's Pill Can Stop HIV. So Why Does Almost Nobody Take It?*, Bloomberg (Feb. 18, 2015), https://www.bloomberg.com/news/articles/2015-02-18/gilead-s-pill-can-stop-hiv-so-why-does-almost-nobody-take-it-/.

[121] My PrEP Experience, *PrEP is a powerful tool in the AIDS response* (May 15, 2014), https://myprepexperience.blogspot.com/2014/05/67-leading-hivaids-groups-endorse-cdc.html.

choice, as part of comprehensive prevention."[122] New York, Washington, D.C., and San Francisco each launched public information campaigns, without any funding from Gilead, recommending the use of Truvada for PrEP.[123]

It was only after Truvada's sales started to soar, due to hard work of community activists and essentially in spite of Gilead, that Gilead finally began to advertise and promote what was clearly a life-saving breakthrough made by the Government's scientists. Gilead first marketed Truvada for PrEP to the public on social media in 2017 and Gilead ran its first advertisement in June 2018—a remarkable delay. Amici can think of no other example where a pharmaceutical company has had the only pharmaceutical available for an entirely new category of drugs (here, HIV prevention), and then completely ignored the new market.

Gilead earned enormous profits on its sales of Truvada for PrEP. At trial, Dr. Grant testified to this resounding commercial success, noting that Gilead has enjoyed sales in excess of $10,000,000,000.[124] Gilead enjoyed a staggering 97% gross profit margin and 83-89% incremental profit margin on PrEP sales.[125]

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[122] *See* World Health Organization, *Global HIV Programme: Pre-exposure prophylaxis (PrEP)*, https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/prevention/pre-exposure-prophylaxis#:~:text=As%20of%20September%202015%2C%20WHO,as%20part%20of%20comprehensive%20prevention (last accessed Dec. 5, 2024).
[123] Michela Tindera, *Gilead Said PrEP To Prevent HIV Was 'Not a Commercial Opportunity.' Now It's Running Ads For It*, (Aug. 8, 2018).
[124] Appx33232.
[125] Appx33277.

The "extensive" and remarkable success of PrEP, both before and after Gilead finally began promoting it commercially, is strong evidence of the invention's "novelty, value, and usefulness." *WBIP*, 829 F.3d at 1337 (quoting *Magowan v. N.Y. Belting & Packing Co.*, 141 U.S. 332, 343 (1891)). Indeed, the commercial success of PrEP applies *a fortiori* where Gilead's windfall profits were earned even after Gilead slow-walked its advertising efforts for PrEP. It is difficult to conceive of a better illustration of how commercial success can demonstrate nonobviousness than a situation where, as here, the infringer *itself* (i) did not invest in the infringing product because it did not believe Truvada would be a successful HIV prevention intervention; (ii) did not invest in promotion of the product until many years after the government's initial work and well after clinical trials proved that Truvada for PrEP was safe and effective for HIV prevention; and (iii) nevertheless earned stunning profits in excess of $10,000,000,000.

CONCLUSION

The search for effective prevention was a road littered with failures. Amici and members of amici lived through this history, witnessed and celebrated the U.S. government's remarkable breakthrough research, and have long advocated for increased access to PrEP, during a period when Gilead did little to nothing to advance HIV prevention. When the government's patents were held invalid, Gilead was not held accountable for its infringement and was able to continue to accrue

billions of dollars in profits, free riding off scientific development conducted and paid for by the U.S. government at great cost to U.S. taxpayers. Amici ask the court to recognize the validity of the government's patents on this remarkable HIV prevention breakthrough so that Gilead can finally be held to account for its longstanding infringement of U.S. government patents.

Respectfully submitted,

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/s/ Laurel Boman

Laurel Boman
Natalie Lesser
Joseph E. Samuel, Jr.
BERGER MONTGUE PC
1818 Market Street, Suite 3600
Philadelphia, PA 19103
(215) 875-3000
lboman@bm.net
nlesser@bm.net
jsamuel@bm.net

Counsel for Amici Curiae PrEP4All, AIDS Action Baltimore, amfAR, AVAC, Housing Works, and Treatment Action Group

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

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