

INNOVATION TO CONTAIN THE HIV/AIDS CRISIS: A TRUVADA CASE STUDY

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I. INTRODUCTION

Look how far we've come This generation hasn't seen all the wasting away and dying that scared the hell out of us years ago. And most people in this generation don't know anyone who has died from the disease. People who are 25–35 don't have a clue what happened when people were dying all around us and the fear and terror of an HIV diagnosis Yes, it's no longer as bad as it once was, yet we still have over 36,000 new HIV transmissions annually here in the U.S. and it's still a major disease globally, and people are

still dying from it. And the science and the disease don't get as much publicity as they used to.¹

—*Dr. Anthony Fauci, 2022.*

Truvada is a story of public health, fundamental research, and the pharmaceuticals industry innovating together to lift the once-deadly curse of the human immunodeficiency virus (HIV). From the early to mid-1980s, fear drove patients with the new and devastating Acquired Immunodeficiency Syndrome (AIDS) condition (and their friends) to organize among themselves, fight for government recognition, and help combat the growing AIDS pandemic. American public health authorities eventually responded to AIDS activism, such as when the U.S. Food and Drug Administration (FDA) made it easier for emergency drugs like AIDS treatments to be quickly approved.

In this period, university chemists Dr. Antonín Holý and Dr. Dennis Liotta were interested in making a mark on antiviral chemistry. Dr. Holý found a powerful anti-HIV medication called tenofovir by stroke of genius and brute force, which would go on to become its own commercialized product and one active ingredient in the combination therapy against HIV called Truvada. Separately, Dr. Liotta found another powerful anti-HIV medication called emtricitabine largely by brute force and serendipity that would become the second active ingredient of Truvada. Two different large pharmaceutical companies licensed these chemists' technologies for product development, but both companies would give up their initial licenses and make room for startup Gilead Sciences to dominate the nascent HIV treatment market. Gilead grew into a behemoth biopharmaceutical company largely because of its breakthrough HIV treatment Truvada, and recently won a unique patent litigation against the Centers for Disease Control and Prevention (CDC) to keep its intellectual property (IP) rights. The story of Truvada captures many different aspects of innovation in the life sciences sector.

II. TECHNICAL PRIMER

The purpose of Truvada is to reduce the likelihood of death (as treatment) and spread (as a preventive) in the ongoing Human Immunodeficiency Virus (HIV) pandemic.² The Truvada technology does this by building on earlier technologies that imitate how human biology builds DNA from RNA. To

1. John Casey, *Dr. Fauci Isn't Going Anywhere Until There's a Cure for HIV*, ADVOCATE (Mar. 24, 2022), <https://www.advocate.com/health/2022/3/24/dr-fauci-isnt-going-anywhere-until-hes-found-cure-hiv>.

2. See U.S. Patent No. 8,592,397 (filed Aug. 20, 2008) (describing in the Abstract the purpose of the claimed chemical composition) [hereinafter '397 Patent].

understand the development story and innovation drivers behind Truvada, this Article first presents technical overviews of the virus and the mechanisms of action for anti-HIV drugs like Truvada.³ Table 1 provides a summary list of all HIV treatments and when they were first approved by the FDA. Appendix 1 summarizes the key events (that are described in detail in the next Part, Part III: Chronology of Innovation) leading to the development of Truvada.

A. HIV: THE RETROVIRUS THAT CAUSES AIDS

The core defense line of the human immune system is the helper T cell.⁴ These kinds of white blood cells help the body kill all kinds of pathogens, including bacteria, viruses, fungi, and cancerous cells.⁵ HIV is devastating because it gradually destroys the body's store of helper T cells, which normally reside in the lymph system. The Supreme Court summarized the mechanism of HIV infection and the resulting prognosis of AIDS in order to weigh whether HIV infection is a disability in *Bragdon v. Abbott*.⁶

Once a person is infected with HIV, the virus invades different cells in the blood and in body tissues T-lymphocytes or CD4+ cells are particularly vulnerable to HIV. The virus attaches to the CD4 receptor site of the target cell and fuses its membrane to the cell's membrane. HIV is a retrovirus, which means it uses an enzyme to convert its own genetic material into a form indistinguishable from the genetic material of the target cell. The virus' genetic material migrates to the cell's nucleus and becomes integrated with the cell's chromosomes. Once integrated, the virus can use the cell's own genetic machinery to replicate itself. Additional copies of the virus are released into the body and infect other cells in turn The virus eventually kills the infected host cell The initial stage of HIV infection is known as acute or primary HIV infection. In a typical case, this stage lasts three months. The virus concentrates in the blood. The assault on the immune system is immediate. The victim suffers from a sudden and serious decline in the number of white blood cells. There is no latency period. Mononucleosis-like symptoms often emerge between six days and six weeks after infection, at times accompanied by fever, headache, enlargement of the lymph nodes (lymphadenopathy), muscle pain (myalgia), rash, lethargy, gastrointestinal disorders, and neurological disorders.

3. *See id.*

4. *See* Bruce Alberts et al., *Helper T Cells and Lymphocyte Activation*, in *MOLECULAR BIOLOGY OF THE CELL* (4th ed. 2002).

5. *See id.*

6. *Bragdon v. Abbott*, 524 U.S. 624, 633–37 (1998) (citations omitted) (defining HIV infection as a disability); *see also* Hassan M. Naif, *Pathogenesis of HIV Infection*, 5 *INFECTIOUS DISEASE REPORTS SUPPL.* 26, 26, 28 (2013) (describing, in depth, the HIV infection mechanism and progression of disease into AIDS if left untreated).

Usually these symptoms abate within 14 to 21 days. HIV antibodies appear in the bloodstream within 3 weeks; circulating HIV can be detected within 10 weeks A person is regarded as having AIDS when his or her CD4+ count drops below 200 cells/mm³ of blood or when CD4+ cells comprise less than 14% of his or her total lymphocytes.

In the summer of 1983, French virologists Drs. Françoise Barré-Sinoussi and Luc Montagnier (hereinafter, “Barré-Sinoussi” and “Montagnier,” respectively), isolated a novel retrovirus⁷ inside AIDS patients’ lymph nodes (where helper T cells most commonly reside).⁸ Similar findings of “lymphocytopathic [lymph-cell-killing] retroviruses” in AIDS patients by American doctors and virologists followed; more than two years into the AIDS pandemic, HIV was identified as its cause.⁹ This finding was consistent with many doctors’ unexplained observations as the AIDS pandemic began: dying AIDS patients appeared to have *no* helper T cells.¹⁰

This precise knowledge of the mechanism and timeline of a typical HIV/AIDS case developed over a decade of research across the globe. Congress launched the first federal legislative action with the Health Omnibus Programs Extension (HOPE) Act of 1988 alongside Reagan’s first executive order on AIDS.¹¹ During a 2012 panel discussion, a world leader in the AIDS pandemic response, Sir Richard Feacham (hereinafter, “Feacham”), remarked that HIV was the most well-studied and well-understood human virus ever in 2000; that year, HIV was also the largest lethal pandemic mankind had ever experienced.¹² At the time of Feacham’s panel discussion in 2012,

7. A retrovirus is a type of virus that has genetic material in the form of RNA. A retrovirus will invade a host cell, insert its RNA genetic material into the host cell’s DNA, and then use its host’s DNA for further replication that is difficult for the host’s immune systems to detect. See *Talking Glossary of Genomic and Genetic Terms: Retrovirus*, NAT’L HUM. GENOME RSCH INST., <https://www.genome.gov/genetics-glossary/Retrovirus> (last visited Mar. 11, 2023).

8. See Barré-Sinoussi et al., *Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)*, 220 SCI. 868 (1983).

9. See Gallo et al., *Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS*, 224 SCI. 500 (1984); see also Levy et al., *Isolation of Lymphocytopathic Retroviruses from San Francisco Patients with AIDS*, 225 SCI. 840 (1984).

10. RANDY SHILTS, AND THE BAND PLAYED ON: POLITICS, PEOPLE, AND THE AIDS EPIDEMIC 42, 72 (2013).

11. See, e.g., 42 U.S.C. § 300cc (describing government programs and their statutory requirements enacted in 1988 onwards for research with respect to AIDS, including establishing the NIH’s Office for AIDS Research and AIDS Research Advisory Committee).

12. See THE EVOLUTION OF HIV/AIDS THERAPIES (Chemical Heritage Foundation & Science History Institute 2012), <https://vimeo.com/59281508> (containing clip of Sir Richard Feacham, founder of the Global Fund, sharing the contrast between sheer knowledge of HIV scientifically against the lack of action in the early years, beginning at the 27 minute mark).

approximately 25–35 million people had died of AIDS-related illnesses worldwide, and recently the UN estimated 32.9–51.3 million dead of AIDS-related illnesses as of 2021.¹³

B. ANTIRETROVIRAL TECHNOLOGY FOR HIV INHIBITION

Antiretroviral therapy (ART) technology has been at the heart of the public health response to the HIV/AIDS pandemic since the 1980s. To understand Truvada and the value it adds in this field, this Section first covers ART technologies in general and then covers the technology of Truvada.

1. *Antiretroviral Therapies for HIV*

The very first ART to mitigate HIV infection came on the market in 1987.¹⁴ This class of drugs—normally taken orally—has become the staple treatment for HIV infection. More recently, several ARTs are also staple preventive therapies for at-risk populations. The goal of all ART treatments, which may be given in combination as highly active antiretroviral therapy (HAART) to match each case’s severity, is to halt HIV replication and to prevent the patient from developing AIDS.¹⁵

The National Cancer Institute collaborated with the Burroughs-Wellcome Company to invent the first treatment to slow HIV progression—azidothymidine (AZT).¹⁶ This collaboration to develop AZT began decades earlier in search of an anti-cancer therapeutic.¹⁷ AZT was first FDA approved for HIV treatment in 1987,¹⁸ while Burroughs-Wellcome filed five patents that were later granted to give them a monopoly that restricted therapy access to those who could afford expensive medication.¹⁹

13. See *Global HIV & AIDS Statistics – Fact sheet*, UNAIDS, <https://www.unaids.org/en/resources/fact-sheet> (last visited Feb. 16, 2024).

14. See National Institutes of Health, *Antiretroviral Drug Discovery and Development*, NIAID, <https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development#:~:text=In%20March%201987%2C%20AZT%20became,reverse%20transcriptase%20inhibitors%2C%20or%20NRTIs> (last visited Mar. 11, 2023).

15. See *id.*

16. See *In Their Own Words... NIH Researchers Recall the Early Years of AIDS*, NAT’L INST. HEALTH, <https://history.nih.gov/display/history/In+Their+Own+Words> (last visited Sept. 11, 2022).

17. See *id.*

18. See *id.*

19. See Malcolm Gladwell, *LAW SUIT ON AIDS-DRUG PATENT SEEKS TO END FIRM’S MONOPOLY*, WASH. POST (Mar. 19, 1991), <https://www.washingtonpost.com/archive/politics/1991/03/20/lawsuit-on-aids-drug-patent-seeks-to-end-firms-monopoly/cf168a7b-b071-4af3-b445-4e1c4274b52b>.

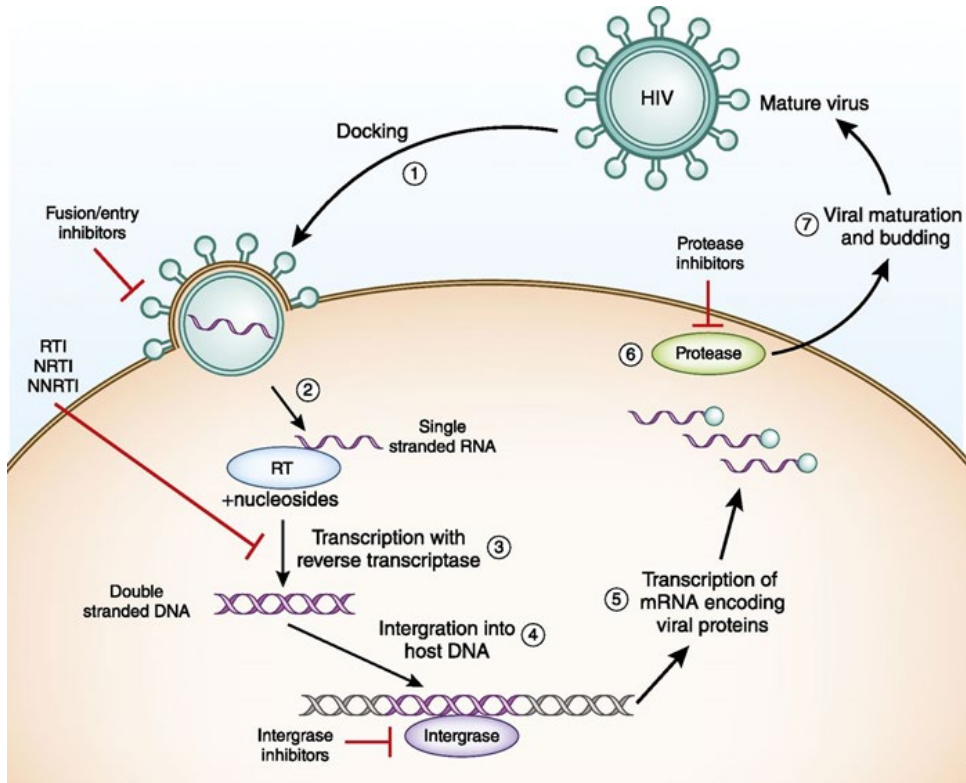
The first HIV treatment was technically successful, but it had many drawbacks. AZT was the first “nucleoside reverse transcriptase inhibitor” (NRTI) against HIV, slowing HIV’s ability to infect host cells by inhibiting the virus’ reverse transcriptase (RT) (an enzyme responsible for creating viral DNA from viral RNA, an essential step to permanently encode and install viral genetic material into the host cell’s DNA).²⁰ However, in the early 1990s, researchers discovered AZT was “highly toxic to human cells” and otherwise difficult for patients to adhere to for their lifetime, so the AIDS innovation ecosystem quickly realized AZT was far from a slam-dunk cure for HIV.²¹ Anger and frustration in the AIDS community (discussed *infra*, Section III.A.3) over AZT’s toxicity and inequitable distribution prompted protests at federal public health authority headquarters and a race to develop better ARTs.²²

20. See Parth H. Patel & Hassam Zulfiqar, *Reverse Transcriptase Inhibitors*, in STATPEARLS (2022), [https://www.ncbi.nlm.nih.gov/books/NBK551504/#:~:text=The%20nucleoside%2Fnucleotide%20reverse%20transcriptase%20inhibitors%20\(NRTIs\)%20were%20the,kinases%20will%20activate%20the%20drug](https://www.ncbi.nlm.nih.gov/books/NBK551504/#:~:text=The%20nucleoside%2Fnucleotide%20reverse%20transcriptase%20inhibitors%20(NRTIs)%20were%20the,kinases%20will%20activate%20the%20drug).

21. David T. Chiu & Peter H. Duesberg, *The Toxicity of Azidothymidine (AZT) on Human and Animal Cells in Culture at Concentrations Used for Antiviral Therapy*, 95 GENETICA 103, 103, 107–08 (1995).

22. See U.S. Department of Health & Human Services, *A Timeline of HIV and AIDS – 1990*, HIV.GOV, <https://www.hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline/#year-1990> (last visited Sept. 11, 2022) [hereinafter *A Timeline of HIV and AIDS*].

Figure 1: Seven-step life cycle of HIV inside and outside of a human cell (orange), showing the mechanisms of HIV inhibition by different anti-retroviral technologies (red lines).²³



The race to find a safer treatment than AZT, and ideally a cure, resulted in an explosion in the 1990s of different ART treatments against HIV coming to market; the types of ART treatment are shown with red lines in Figure 1.²⁴ There are now well over a dozen different ART products (shown in Table 1, *infra*), each of which typically fall into one of six novel categories.

These ART categories include: (1) NRTIs, the first being AZT, as well as nucleotide RT enzyme inhibitors (NtRTIs) that block RT transcription of viral RNA into cellular DNA (shown in step 3 of Figure 1); (2) non-nucleoside RT inhibitors (NNRTIs) that also block RT activity (shown in step 3 of Figure 1); (3) protease inhibitors (PIs) that block viral protein building blocks from

23. See generally Mohamed G. Atta et al., *Clinical Pharmacology in HIV Therapy*, 7 CLINICAL J. AM. SOC'Y NEPHROLOGY 435 (2018) (describing the broad set of HIV antiretroviral technologies, including the NtRTI/NRTI technology deployed by Truvada).

24. See *A Timeline of HIV and AIDS*, *supra* note 22 (explaining further in the section on 1995).

assembling into mature viral particles (shown in step 6 of Figure 1); (4) integrase inhibitors that block incorporation of viral DNA into cellular DNA (shown in step 4 of Figure 1); and (5) entry, fusion, or attachment inhibitors that change the proteins on the cell surface to prevent HIV from inserting viral RNA into the cell (shown in steps 1 and 2 in Figure 1).²⁵ See Figure 1 for the life cycle location upon which each HIV technologies inhibits replication, Table 1 for a list of all currently-marketed ARTs listed by life cycle location, and Table 2 for adverse effects of ARTs again grouped by life cycle location.

Table 1: Anti-retroviral compounds by class and related prodrug forms approved by the FDA.²⁶

ART Class	Compound	Prodrug Forms	U.S. Trade Name	1st FDA Approval
Nucleoside RT enzyme inhibitors (NRTIs) and Nucleotide RT enzyme inhibitors (NtRTIs)	Azidothymidine (AZT) (a/k/a Zidovudine)	--	Retrovir	1987
	2',3'-dideoxy-3'-thiacytidine	Lamivudine ("3TC"); (-)-L-2',3'-dideoxy-3'-thiacytidine	Epivir	1995 (combination ART) 2002 (once-a-day)
		Emtricitabine ("FTC"); 2',3'-dideoxy-5-fluoro-3'-thiacytidine	Emtriva (formerly Coviracil)	2003
	Abacavir (ABC)	--	Ziagen	1998
	Tenofovir	Tenofovir disoproxil fumarate (TDF)	Viread	2004
		Tenofovir alafenamide fumarate (TAF)	Vemlidy	2016
Non-nucleoside RT enzyme inhibitors (NNRTIs)	Nevirapine (NVP)	--	Viramune	1996
	Efavirenz (EFV)	--	Sustiva	1998
	Etravirine (ETR)	--	Intelence	2008
	Rilpivirine (RPV)	--	Edurant	2011 (combination ART)
	Doravirine (DOR)	--	Pifeltro	2018
Integrase inhibitors (INSTIs)	Raltegravir (RAL)	--	Isenstress	2007
	Elvitegravir (EVG)	--	One ingredient in Stribild	2012 (combination ART)
		--	Vitekta	2014 (once-a-day)
Dolutegravir (DTG)	--	Tivicay	2013	

25. Roger Pebody, *Types of antiretroviral medications*, NAM AIDSMAP (May 2021), <https://www.aidsmap.com/about-HIV/types-antiretroviral-medications>.

26. See *id.*; see also U.S. Food & Drug Administration, *FDA-Approved Drugs*, DRUGS@FDA, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> (providing searchable database containing FDA approval letters for each drug, containing approval dates and any toxicity concerns).

ART Class	Compound	Prodrug Forms	U.S. Trade Name	1st FDA Approval
	Bictegravir (BIC)	--	Only in a HAART called Biktarvy	2018
	Cabotegravir (CBG)	--	Apretude	2021 (injection every 2 months)
			Vocabria	2021 (once-a-day)
			One ingredient in Cabenuva	2021 (combination ART)
Entry inhibitors (EIs)	Enfuvirtide (ENF)	--	Fuzeon	2003
	Maraviroc (MVC)	--	Selzentry	2007
Protease inhibitors (PIs)	Lopinavir (LPV)	--	One ingredient in Kaletra	2000
	Atazanavir (ATV)	--	Reyataz	2003 (once-a-day)
			One ingredient in Evotaz	2015 (combination ART)
	Darunavir (DRV)	--	One ingredient in Prezista	2006 (combination ART)
One ingredient In Prezcobix			2015 (single-tablet combination)	
Attachment inhibitors (CIs)	Ibalizumab (IBA)	--	Trogarzo	2018 (for ART-resistant patients)
	Fostemsavir (FTR)	--	Rukobia	2020 (for ART-resistant patients)
PI Boosters (also known as "PK Boosters")	Ritonavir (RTV)	--	Second ingredient in Kaletra	2000
			Norvir	2004
	Cobicistat (COBI)	--	Tybost	2014

Table 2: Known risks of adverse effects of treatment by ART class and individual compound.²⁷

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIs
Bone Density Effects	TDF: Associated with greater loss of BMD than other NRTIs, especially when given with a PK booster. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. TAF: Associated with smaller declines in BMD than those seen with TDF.	Decreases in bone mineral density (BMD) observed after the initiation of any ART regimen			N/A	Not evaluated

27. National Institutes of Health, *Limitations to Treatment Safety and Efficacy – Adverse Effects of Antiretroviral Agents*, HIV.GOV, <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/adverse-effects-antiretroviral-agents> (last visited May 20, 2023).

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIIs
Bone Marrow Suppression	ZDV: Anemia, neutropenia	N/A	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A	RPV and EFV: QTc prolongation (a potential form of heart arrhythmia).	ATV/r and LPV/r: PR prolongation (a potential form of heart arrhythmia). Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation	N/A	FTR: QTc prolongation was seen at four times the recommended dose. Use with caution in patients with pre-existing heart disease or QTc prolongation, or concomitant use of medications that may prolong QTc interval.	N/A
Cardiovascular Disease (CVD)	ABC: Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	Boosted DRV and LPV/r: Associated with cardiovascular events in some cohorts	N/A	N/A	N/A
Cholelithiasis	N/A	N/A	ATV: Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	N/A	N/A	N/A
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A	N/A
Dyslipidemia	ZDV > ABC: ↑ Triglycerides (TG) and ↑ low-density lipoprotein cholesterol (LDL). TAF: ↑ TG, ↑ LDL, and ↑ high-density lipoprotein cholesterol	EFV: ↑ TG, ↑ LDL, ↑ HDL	All RTV- or COBI-Boosted PIs: ↑ TG, ↑ LDL, ↑ HDL LPV/r > DRV/r and ATV/r: ↑ TG	EVG/c: ↑ TG, ↑ LDL, ↑ HDL	N/A	N/A

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIIs
	(HDL) (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.					
Gastrointestinal Effects	ZDV > Other NRTIs: Nausea and vomiting	N/A	Gastrointestinal (GI) intolerance (e.g., diarrhea, nausea, vomiting) LPV/r > DRV/r and ATV/r. Diarrhea	EVG/c: Nausea and diarrhea	N/A	LEN: Nausea and diarrhea
Hepatic Effects	When TAF, TDF, 3TC, and FTC are withdrawn in Patients with Hepatitis B (HBV) and HIV Coinfection or when HBV Resistance Develops: Patients with HBV/HIV coinfection may develop severe hepatic flares. ZDV: Steatosis	EFV: Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm ³ and men with pre-NVP CD4 counts >400 cells/mm ³ . NVP should never be used for post-exposure prophylaxis. EFV and NVP are not recommended in patients with hepatic	All PIs: Drug-induced hepatitis and hepatic decompensation have been reported. ATV: Jaundice due to indirect hyperbilirubinemia	DTG: Persons with HBV or Hepatitis C (HCV) coinfection may be at higher risk of DTG-associated hepatotoxicity.	MVC: Hepatotoxicity with or without rash or hypersensitivity reactions (HSRs) has been reported. FTR: Transaminase elevation was seen more commonly in patients with HBV/HCV. Transient elevation of bilirubin observed in clinical trials.	N/A

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIIs
		insufficiency (Child-Pugh class B or C).				
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	ABC: Contraindicated if patient is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within six weeks. HSR Symptoms (in Order of Descending Frequency): Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	NVP: Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy Risk is greater for ARV-naïve women with pre-NVP CD4 counts >250 cells/mm ³ and men with pre-NVP CD4 counts >400 cells/mm ³ . Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	RAL: HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. DTG: Reported in <1% of patients in clinical development program	MVC: HSR reported as part of a syndrome related to hepatotoxicity.	N/A
Injection Site Reaction		RPV IM Injection: Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.		CAB IM Injection: Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.	T-20 SQ Injection: Reported in almost all patients; reactions may include pain, tenderness, nodules, induration, ecchymosis, erythema.	LEN SQ injection: Reported in 47–62% of patients; reactions may include swelling, erythema, pain, nodules, inflammation, induration. Nodules and induration

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIIs
						may persist for months in some patients.
Lactic Acidosis	Reported with Older NRTIs, d4T, ZDV, and ddI, but not with ABC, 3TC, FTC, TAF, or TDF.	N/A	N/A	N/A	N/A	N/A
Lipodystrophy	Lipoatrophy: Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, or TAF or TDF.	Lipohypertrophy: Trunk fat increase is observed with EFV-, PI-, and RAL-containing regimens; however, a causal relationship has not been established.			N/A	N/A
Myopathy / Elevated Creatine Phosphokinase	ZDV: Myopathy	N/A	N/A	RAL and DTG: ↑ creatine phosphokinase (CPK), rhabdomyolysis, and myopathy or myositis have been reported.	N/A	N/A
Nervous System / Psychiatric Effects	History of Exposure to ddI, ddC, or d4T: Peripheral neuropathy (can be irreversible)	Neuropsychiatric Events: EFV > RPV, DOR, ETR EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. [. . .] RPV: Depression, suicidality, sleep disturbances	N/A	All INSTIs: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre- existing psychiatric conditions.	N/A	LEN: Headache

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIIs
		DOR: Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality, and self-harm				
Rash	FTC: Hyperpigmentation	All NNRTIs	ATV, DRV, and LPV/r	All INSTIs	MVC, IBA, FTR	N/A
Renal Effects / Urolithiasis	TDF: ↑ Bloodserum creatinine (SCr), proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. TAF: Less impact on renal biomarkers and lower rates of proteinuria than TDF	RPV: Inhibits creatinine (Cr) secretion without reducing renal glomerular function	ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. ATV: Stone or crystal formation; adequate hydration may reduce risk COBI (as a Boosting Agent for DRV or ATV): Inhibits Cr secretion without reducing renal glomerular function	DTG, COBI (as a Boosting Agent for EVG), and BIC: Inhibits Cr secretion without reducing renal glomerular function	IBA: SCr abnormalities ≥Grade 3 reported in 10% of trial participants. FTR: SCr > -1.8 x Upper Limit Normal (ULN) seen in 19% in a clinical trial, but primarily with underlying renal disease or other drugs known to affect creatinine.	N/A
Stevens-Johnson Syndrome / Toxic Epidermal Necrosis	N/A	NVP > EFV, ETR, RPV	Some reported cases for DRV, LPV/r, and ATV	RAL	N/A	N/A
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF and with DOR than with EFV.			INSTI > other ARV drug classes	N/A	N/A

As Figure 1 shows, each type of ART uses a different mechanism to block HIV replication. But individual active ingredients (as listed in Table 1) differ in their properties, e.g., uptake efficiency (“bioavailability”) or long-term

toxicity concerns; Table 2 lists toxicity concerns by drug class. To mitigate these concerns, many of these compounds have been modified with additional chemical groups to form prodrugs.²⁸ A further approach combines multiple ART active ingredients to create a combined ART against HIV,²⁹ as is the case with Truvada (“Truvada”) and Truvada for PrEP (“Truvada for PrEP”).³⁰

2. *Truvada Technology Overview*

Truvada is a combination of two antiretroviral technologies: (1) tenofovir disoproxil fumarate and (2) emtricitabine. The technology behind each is described in this Section.

a) Technical Overview of Tenofovir Disoproxil Fumarate

The first component of Truvada,³¹ tenofovir, acts to inhibit HIV infection³² like AZT: both disrupt HIV RT transcription of viral RNA to DNA in the host cell. Viral RT recognizes tenofovir as a natural nucleotide (a building block of DNA).³³ But, tenofovir differs from a natural nucleotide in a key way: it lacks the functional group (the 3'-hydroxyl group) that RT uses to chemically join one nucleotide to another in a growing DNA chain. Thus, when RT incorporates tenofovir in the growing DNA strand, instead of building a natural nucleotide, viral DNA transcription halts pre-maturely. This antiretroviral activity is an example of a NtRTI, also referred to as “nucleotide analog[] reverse transcriptase inhibitor” (shown in Figure 1, *supra*) (emphasis added).³⁴ Nucleoside reverse transcriptase inhibitors, like AZT, differ slightly in chemical structure but halt DNA transcription by the same mechanism.

28. See generally M. S. Palombo et al., *Prodrug and Conjugate Drug Delivery Strategies for Improving HIV/AIDS therapy*, 19 J. DRUG DELIVERY SCI. & TECH. 3, 3–14 (2009) (describing the mechanisms by which many different modifications to known antiretroviral drugs as “prodrugs” had been made to improve HIV eradication).

29. See *Antiretroviral Therapy*, PAN AM. HEALTH ORG., <https://www.paho.org/en/topics/antiretroviral-therapy> (last visited Nov. 5, 2022).

30. *Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021752s000_TruvadaTOC.cfm (last visited Sept. 11, 2022).

31. See *id.*

32. See '397 Patent, *supra* note 2, at col. 2:15–19.

33. See *id.* at col. 1:20–29 (describing weaknesses of the first HIV reverse transcriptase inhibitors, including AZT, in terms of its toxicity and susceptibility to viral resistance); see also *id.* at col. 7:52–55 (“Tenofovir disoproxil fumarate (DF) is a nucleotide reverse transcriptase inhibitor.”); see also Eric J. Arts and Daria J. Hazuda, *HIV-1 Antiretroviral Drug Therapy*, 2 COLD SPRING HARBOR PERSPS. MED. a007161, 7 (2012).

34. Parth H. Patel & Hassam Zulfiqar, *Reverse Transcriptase Inhibitors*, in STATPEARLS (2023) (describing the chemistry of nucleotide- and nucleoside-reverse transcriptase inhibitors

Tenofovir disoproxil fumarate (TDF) is a “prodrug” of the molecule tenofovir that is metabolized in the body into its active form.³⁵ Prodrugs can improve delivery of the active ingredient when the active form cannot efficiently enter target cells or metabolic processes degrade it before it can achieve sufficient therapeutic effect.³⁶ Since TDF helps the body get tenofovir where it needs to go and TDF shows improved efficacy over pure tenofovir when taken orally, many HIV combination therapies transitioned to include TDF.

b) Technical Overview of Emtricitabine

The second component of Truvada, emtricitabine, has a similar yet distinct mechanism of inhibiting HIV replication and infection.³⁷ Emtricitabine acts like AZT as a “nucleoside analog reverse transcriptase inhibitor (NRTI; see Figure 1, *supra*),” specifically imitating the nucleoside known as cytosine, another of the four fundamental building blocks of DNA and RNA.³⁸ As a nucleoside-impersonating inhibitor of the RT enzyme, emtricitabine works by entering into the RT enzyme’s produced viral genome, “causing [early] termination” of the produced viral DNA, and ultimately rendering the viral DNA defective.³⁹

Therefore, in combination, the two components of Truvada (TDF and emtricitabine) heavily inhibit the virus’ RT by posing to the enzyme as defective analogs of two of the four DNA building blocks.⁴⁰ In this way, Truvada relies more heavily than other ARTs on RT inhibition (shown in Figure 1, *supra*) for the life cycle of HIV in human cells and where current medicines including NtRTIs and NRTIs like those in Truvada are used).⁴¹

in the Mechanism of Action section); *see also* Peter L. Anderson et al., *The Cellular Pharmacology of Nucleoside- and Nucleotide-Analogue Reverse-Transcriptase Inhibitors and Its Relationship to Clinical Toxicities*, 38 *CLINICAL INFECTIOUS DISEASES* 743, 745 (2004) (describing the TDF metabolic pathway as an adenosine nucleotide analog in the source’s Figure 1).

35. *See* ’397 Patent, *supra* note 2, at col. 6:64–67.

36. *See id.* at col. 4:40–51; *see also* Jarkko Rautio et al., *The Expanding Role of Prodrugs in Contemporary Drug Design and Development*, 17 *NATURE REVIEWS. DRUG DISCOVERY* 559 (2018) (explaining why and how prodrugs are commonly used to develop treatments in the modern pharmaceutical industry).

37. *See* ’397 Patent, *supra* note 2, at col. 9:1–39.

38. *See* E. Paintsil, Yung-Chi Cheng, *Antiviral Agents*, in *ENCYCLOPEDIA MICROBIOLOGY* 249 (3d ed. 2009).

39. *Id.*

40. *See* FDA, *Truvada® Package Insert* (rev. June 2020) at 1, https://www.gilead.com/~/media/files/pdfs/medicines/HIV/truvada/truvada_pi.pdf.

41. *See generally* Mohamed G. Atta et al., *Clinical Pharmacology in HIV Therapy*, *CLINICAL J. AM. SOC’Y NEPHROLOGY* (2018) (describing the broad set of HIV antiretroviral technologies, including the NtRTI/NRTI technology deployed by Truvada).

Truvada is effective: Long-term use often reduces patients' HIV load to "undetectable" levels (the first approved clinical indication for Truvada) and therefore stops progression to AIDS.⁴² After a potential HIV exposure emergency, use of Truvada short-term with other ART(s) can prevent infection as a "post-exposure prophylactic" (PEP). Alternatively—and more commonly—routine or continuous "pre-exposure prophylactic" (PrEP) use of Truvada alone (the second approved clinical indication for Truvada) reduces HIV infection risk by as much as 99%.⁴³

III. CHRONOLOGY OF INNOVATION

The innovations behind Truvada span more than three decades of collaboration among public and private health institutions, largely driven by the suffering and tenacity of AIDS patients. Appendix 1 at the end of this Article provides a summary table of key events in the Truvada innovation story. This story begins with the medical community's identification of the disease in the early 1980s, after the disease had slowly circulated in sub-Saharan Africa for years. In the first years of the HIV/AIDS pandemic, federal health authorities failed to act. HIV/AIDS patients and friends turned to activism and changed the way U.S. public health agencies work to serve their constituents. These activists built a novel international coalition of philanthropic organizations, clinicians, universities, federal health authorities, and large and small pharmaceutical companies to hear their concerns and build better treatments. Private and public actors in this coalition patented their technologies as they progressed, enabling a structure of licensing and acquisitions that facilitated the development of Truvada.

Each of the two active ingredients of Truvada, tenofovir and emtricitabine, were developed by university chemists looking to satisfy the unmet need for effective-yet-safe, once-daily anti-HIV medicines. The two Truvada active ingredients were each developed when large pharmaceutical companies shut down HIV treatment development and their HIV research leaders subsequently left for startup companies to address the painful AIDS crisis. The

42. See *Truvada*[®] *Package Insert*, *supra* note 40, at 30 (describing key clinical trial for Truvada for HIV treatment where 84% of the Truvada treatment group achieved < 400 HIV RNA copies/mL of blood, close to the CDC's current definition of "undetectable" as < 200 HIV RNA copies/mL of blood); see also *HIV Treatment as Prevention*, CDC, <https://www.cdc.gov/HIV/risk/art/index.html> (last visited Nov. 13, 2022) (defining "undetectable" HIV viral load as < 200 HIV RNA copies/mL of blood).

43. See *About PEP*, CDC (July 12, 2022), <https://www.cdc.gov/HIV/basics/pep/about-pep.html> (describing PEP for emergency treatment after an HIV exposure event); see also CDC, *PrEP Effectiveness*, <https://www.cdc.gov/HIV/basics/prep/prep-effectiveness.html> (last visited Nov. 13, 2022) (describing PrEP's clinical strengths in containing HIV spread).

two ingredients used together in the product Truvada proved a powerful anti-HIV combination therapy that enables those with HIV to live a full life; later, it became the first medicine with FDA approval to *prevent* HIV infection. Through success with Truvada, its development company Gilead Sciences, Inc. grew into the world's dominant anti-HIV drug manufacturer.

A. PHASE I—BEFORE TRUVADA: HIV/AIDS PANDEMIC EMERGES AND THE WORLD SLOWLY RESPONDS

In the 1980s, AIDS emerged among disadvantaged communities across the world, but governments were very slow to respond. HIV was identified as its cause several years into the pandemic, which provided a technological foothold for the world to begin systematically containing the virus' exponential spread by developing testing, treatments, and vaccines. The magnitude of death and suffering prompted AIDS patients and friends to build activist organizations that pushed U.S. public health authorities to rethink their approach to public health and form an innovation coalition with many public and private actors. This time provides foundational context for the development of Truvada in the late 1980s and 1990s.

1. *Mysterious Disease Slowly Destroyed Communities “and the Band Played On”*

Early in the summer of 1981, five gay men were hospitalized in Los Angeles with a rare combination of bacterial *Pneumocystis carinii* pneumonia and other opportunistic infections that ultimately killed the men within weeks of each other.⁴⁴ These were the first widely known cases of a novel, unidentified disease that would kill at least 130 people in the United States in 1981.⁴⁵ The death toll increased by a factor of four to almost 560 confirmed dead over the next two years before researchers identified the agent causing the disease.⁴⁶

The disease, which quickly became known as “AIDS,” had been circulating in sub-Saharan Africa since the 1950s.⁴⁷ The first cases in the United States and Europe were concentrated in travel medicine practitioners, Black youth, gay men of all ages, and hemophiliacs.⁴⁸ However, by the middle of 1983, 72%

44. See U.S. Dep't Health & Hum. Servs., *A Timeline of HIV and AIDS*, HIV.GOV, <https://www.hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline> (last visited Sept. 11, 2022).

45. *Id.*

46. *Id.*

47. See generally Michael Worobey et al., *Direct Evidence of Extensive Diversity of HIV-1 in Kinshasa by 1960*, 455 NATURE 661, 661–64 (2008) (showing the likelihood of HIV-1 circulating in humans in the 1910s).

48. See *A Timeline of HIV and AIDS*, *supra* note 22.

of the 1,100 AIDS cases in the United States were reported in gay men.⁴⁹ At this time, no one had a scientific understanding of the cause, so many cases went unreported. Nor was there any cure, or even a promising treatment; fear overcame these communities as many faced drawn-out deaths to AIDS.⁵⁰

The U.S. federal government was slow to fund or otherwise support research to understand AIDS as the pandemic grew. The government did not approve any AIDS research grants in 1981–82, despite \$8 million in Congressional appropriations for that purpose.⁵¹ Over \$55 million in proposed projects on AIDS research were submitted to the National Institutes of Health alone during this time.⁵² A leader of the grassroots fight against AIDS compared this failure to launch needed AIDS research to the \$10 million spent in a matter of weeks by the same federal health authorities to respond to the seven Tylenol poisonings in Chicago that same year, screaming in ink, “[w]e desperately need something from our government to save our lives, and we’re not getting it.”⁵³ It took four years of the pandemic raging before President Reagan publicly addressed its existence to a reporter in 1985 and two more years for him to issue the nation’s first executive order to tackle the AIDS pandemic in 1987.⁵⁴

2. *The World’s Early Technologies Against HIV/AIDS*

Researchers’ first steps to contain the pandemic were to develop: (1) identification and testing methods for the pathogen that causes AIDS; (2) vaccines; and (3) effective treatments for HIV-positive patients. Only the first and third of these technologies initially resulted in meaningful HIV containment during first decade of the pandemic: the 1980s and early 1990s. This Section will describe each of the three technology fronts in that time.

a) Identification and Testing of HIV from Patient’s Blood

French virologists Barré-Sinoussi and Montagnier at the Institut Pasteur in France collaborated with Dr. Robert Gallo (hereinafter, “Gallo”) at the U.S. National Cancer Institute (NCI) in the first three years of the pandemic to

49. See Larry Kramer, *1,112 and Counting*, 59 N.Y. NATIVE (1983).

50. *Id.*

51. *Id.*

52. *Id.*

53. *Id.*

54. Joseph Bennington-Castro, *How AIDS Remained an Unspoken—But Deadly—Epidemic for Years*, HISTORY (updated Aug. 22, 2023), <https://www.history.com/news/aids-epidemic-ronald-reagan>; President Ronald Reagan, *Remarks at the American Foundation for AIDS Research Awards Dinner*, AM. PRESIDENCY PROJECT (May 31, 1987), <https://www.presidency.ucsb.edu/documents/remarks-the-american-foundation-for-aids-research-awards-dinner> [hereinafter President Reagan’s Remarks at 1987 AIDS Research Awards Dinner].

identify HIV as the cause of AIDS.⁵⁵ After identifying HIV as a retrovirus that attacks lymphocytes, specifically T cells, each set of scientists raced to publish their findings and develop HIV test kits.⁵⁶ Barré-Sinoussi and Montagnier published their initial findings first in 1983. Gallo published one year later in 1984.⁵⁷

HIV testing prompted an international patent and contract dispute. Barré-Sinoussi and Montagnier collaborated to file a U.S. patent on the first HIV antibody test kit in December 1983, just months after their ultimately-Nobel-prize-winning identification of HIV.⁵⁸ That summer, the Institut contracted with Gallo at NCI to collaborate and provide materials from Barré-Sinoussi's and Montagnier's innovative identification work. Gallo filed his own U.S. patent application on HIV antibody test kits in April 1984, just five months after Montagnier. Gallo's patent application granted while Montagnier's did not.⁵⁹ Gallo and collaborators at the U.S. Department of Health and Human Services went on to develop and mass produce HIV test kits, but initially did not share royalties with the Institut.⁶⁰ The Institut sued the United States for breach of contract to recover royalties. Simultaneously, the Institut pursued separate tort and Freedom of Information Act suits. To resolve these legal disputes, then-President Reagan and French Prime Minister Jacques Chirac negotiated an agreement to share inventorship and royalties for the HIV test kits and to create a new international AIDS foundation.⁶¹ In 1987, Reagan announced jointly with Chirac the financial details of the plan and settlement:⁶²

55. See Barré-Sinoussi, *supra* note 8; Gallo, *supra* note 9; see also Deborah M. Barnes, *AIDS Patent Dispute Settled*, 236 SCI. 17 (1987) (describing collaboration among the scientists for their respective studies).

56. See Barnes, *supra* note 55.

57. *Id.*

58. *Id.*

59. See *id.*

60. See *id.*; see also HIV/AIDS Glossary: Enzyme-Linked Immunosorbent Assay (ELISA), CLINICAL INFO HIV.GOV, <https://clinicalinfo.hiv.gov/en/glossary/enzyme-linked-immunosorbent-assay-elisa> (last visited Feb. 16, 2024) (describing the French-American breakthrough invention for HIV testing).

61. See Barnes, *supra* note 55; see also *Pasteur v. United States*, 814 F.2d 624 (Fed. Cir. 1987) (reversing lower court's decision that French scientists did not state claim in HIV identification and patent dispute, prompting settlement between President Reagan and President Mitterrand to HIV test kit license terms).

62. President Ronald Reagan, *Remarks Announcing the AIDS Research Patent Rights Agreement Between France and the United States*, AM. PRESIDENCY PROJECT (Mar. 31, 1987), <https://www.presidency.ucsb.edu/documents/remarks-announcing-the-aids-research-patent-rights-agreement-between-france-and-the-united> [hereinafter President Reagan's Remarks on AIDS Testing Patent Settlement].

The two medical groups will share the patent, and each party will contribute 80 percent of the royalties received to establish and support an international AIDS research foundation. This foundation, which will also raise private funds, will sponsor AIDS-related research and will donate 25 percent of the funds that they receive to education and research of AIDS problems in less developed countries.

When the French-American HIV test kits became broadly available in the United States in the mid-1980s, the focus in the burgeoning HIV/AIDS research field shifted to treatments for the millions already infected, as well as public health messaging to slow the spread.⁶³

b) Early Failures: AZT and HIV Vaccines

Failure was a common and frustrating feature of early public health attempts to treat or prevent HIV. In the 1990s, at least one researcher published the conclusion that the first ART treatment against HIV—AZT (described in Section II.B: Antiretroviral Technology, *supra*)—was “highly toxic to human cells” and difficult for patients to adhere to the prescribed dosing for their lifetimes.⁶⁴

Separately, vaccine trials began in earnest the same year AZT went to market in 1987, with the National Institutes for Allergy and Infectious Diseases leading the first vaccine trial to prevent AIDS.⁶⁵ In 2004, the international alliance known as The Group of Eight, or “G8,” set forth a call to establish a Global HIV Vaccine Enterprise.⁶⁶ However, despite worldwide spending of more than \$500 million on HIV/AIDS vaccine research almost every year since 2000, researchers have yet to develop an effective HIV vaccine.⁶⁷

c) Therapies After AZT

Scientists considered many different combinations of compounds with anti-retroviral activity to achieve HIV treatment goals: an ART that would (1) change HIV/AIDS from a death sentence to a manageable chronic disease; (2) perform (1) without reducing the life expectancy of the patient due to ART

63. See *A Timeline of HIV and AIDS*, *supra* note 22.

64. Chiu & Duesberg, *supra* note 21, at 107–08.

65. See *In Their Own Words*, *supra* note 16.

66. G8 Sea Island Summit 2004, *G8 Action to Endorse and Establish a Global HIV Vaccine Enterprise*, in UNIV. TORONTO G8 INFO. CTR., <http://www.g8.utoronto.ca/summit/2004seaisland/hiv.html> (last visited Sept. 11, 2022).

67. See Jeffrey E. Harris, *The Repeated Setbacks of HIV Vaccine Development Laid the Groundwork for SARS-CoV-2 Vaccines* (Nat'l Bureau Econ. Rsch, Working Paper No. 28587, 2021).

toxicity; and (3) improve adherence to ART regimens with once-a-day dosing to avoid viral resistance to the drugs.⁶⁸ Truvada succeeded because it largely achieved all of these goals where its ART competitors had not (discussed *infra*, Section III.C).⁶⁹

3. *The Collaboration and Competition Ecosystem for Anti-HIV Treatments*

As the AIDS crisis unfolded in the 1980s and early 1990s in the United States, federal health and innovation agencies, AIDS community activists, universities, small and large pharmaceutical companies, as well as large philanthropies worked to create therapeutic options.

a) The Role of the U.S. Executive Branch and Federal Agencies

U.S. federal health authorities gradually became leaders in responding to the AIDS crisis through special projects and newly created divisions (several of which are highlighted in Table 3 below) to specifically to combat the growing pandemic:

68. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, (Chemical Heritage Foundation & Science History Institute 2012), <https://vimeo.com/59281508> (containing clip of Norbert Bischofberger, EVP of R&D at Gilead Sciences, sharing motivations and goals for Atripla and Truvada for HIV treatment at the 20-minute mark).

69. *Id.*

Table 3: Sample of U.S. federal agency actions in response to AIDS crisis.

Agency	Example Action(s) in Response to AIDS Crisis
NIH	Began approving AIDS research grants in 1983. ⁷⁰
NIAID	Maintained from 1984 onward, at Dr. Anthony Fauci's direction, a special AIDS division to engage in outreach and long-term studies of the HIV/AIDS population. ⁷¹
CDC	Closely monitored the spread of the virus, developed treatment resources, and began to engage in co-coordination of international clinical trial projects. ⁷²
FDA	Approved AZT in 1987 on accelerated basis due in part to AIDS community cries for help. ⁷³
Presidents' Executive Actions	Reagan: used executive orders in 1987–88 to motivate Congress to appropriate the first federally legislated AIDS research funding programs, ⁷⁴ including the NIH's Institute for AIDS Research. ⁷⁵
	George W. Bush: secured in 2004 Congressional approval to create PEPFAR, the President's Emergency Program For AIDS Relief, to combat the pandemic by funding the equitable distribution of HIV treatments to developing nations globally. ⁷⁶
USPTO	Created a centralized AIDS Patent Project in the 1990s to facilitate global knowledge-sharing related to AIDS treatments and research together with the European and Japan Patent Offices. ⁷⁷
	Launched in the 2010s the Patents for Humanity acceleration & awards project, which has included HIV/AIDS technologies, among others. ⁷⁸

70. See Kramer, *supra* note 49.

71. See NIH.gov, *In Their Own Words... NIH Researchers Recall the Early Years of AIDS: Mobilizing*, <https://history.nih.gov/display/history/Mobilizing> (last visited Nov. 13, 2022).

72. See *A Timeline of HIV and AIDS*, *supra* note 48.

73. See National Institutes of Health, *In Their Own Words... NIH Researchers Recall the Early Years of AIDS: Anthony S. Fauci, M.D. – Transcript of Interview 03* at 19, <https://history.nih.gov/display/history/Dr.+Anthony+S.+Fauci+Transcript?preview=/8881339/8881336/Fauci93.pdf> (last accessed Apr. 8, 2024).

74. See President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54.

75. See 42 U.S.C. § 300cc.

76. See *A Timeline of HIV and AIDS*, *supra* note 48.

77. See USPTO, *1996 Annual Review – Our Progress*, USPTO.GOV (1996), <https://www.uspto.gov/about-us/performance-and-planning/annual-reports/1996-annual-review-our-progress> (last visited Nov. 19, 2022).

78. See USPTO, *Patents for Humanity*, USPTO.GOV (2022), <https://www.uspto.gov/ip-policy/patent-policy/patents-humanity> (last visited Nov. 19, 2022).

b) The Role of International Government and Philanthropic Institutions

Global governmental and philanthropic organizations have also been a core part of the AIDS treatment innovation ecosystem.⁷⁹

In the late 1990s, it became clear that ARTs were not reaching developing countries heavily hit by the HIV/AIDS pandemic, especially those in sub-Saharan Africa.⁸⁰ UNAIDS, the United Nations' strategic response team to the pandemic, launched in 1996 to address this concern.⁸¹ The 2000 International AIDS Conference, held in South Africa, highlighted tensions about how to resolve this issue: the international healthcare philanthropic organization *Médecins Sans Frontières* was quietly working with developing countries' leaders to find ways to send them HIV/AIDS medicine at heavy, under-the-table discounts to respond to the rising humanitarian crisis.⁸² HIV/AIDS leaders from the United States and Europe called for a transparent approach—for well-resourced nations to openly fund and facilitate the delivery of critical anti-HIV treatments in developing nations. Within four years, two philanthropic agencies were created for this purpose: the Global Fund (largely based on funds from the United Kingdom and other parts of Europe) formed in 2001 and PEPFAR formed in 2004.⁸³

International organizations also played policymaking and philanthropic roles in the AIDS treatment space. Responding to that contentious 2000 International AIDS Conference, the World Trade Organization (WTO)'s 2001 Fourth Ministerial Conference addressed the rights of nations to access critical medicines under the WTO's 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) through the 2001 Doha Declaration on TRIPS and Public Health.⁸⁴ The Doha Declaration provided that every WTO member state “has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted,” where any granted “compulsory licence” is a demand by a member state for delivery of the public health technology (such as HIV/AIDS treatments) without

79. See THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (describing at the thirty minute mark rationale for creation of the Global Fund and PEPFAR).

80. *Id.*

81. See UNAIDS, *Who We Are: Saving Lives, Leaving No One Behind*, UNAIDS.ORG, <https://www.unaids.org/en/whoare/about> (last visited Nov. 21, 2022).

82. See THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (describing at the thirty minute mark rationale for creation of the Global Fund and PEPFAR).

83. *Id.*

84. See WTO, *Declaration on the TRIPS Agreement and Public Health*, DOHA DECLARATIONS at 24-25, https://www.wto.org/english/res_e/booksp_e/ddec_e.pdf (last visited Nov. 21, 2022).

negotiation with the intellectual property owner.⁸⁵ The Doha Declaration brought the world's governments to the collaboration table with HIV/AIDS research and treatment innovators and businesses.⁸⁶

Lastly, non-governmental philanthropies played a key role in enabling HIV/AIDS treatment development, including Truvada (described in Phases II and III, *infra*, Sections III.B and III.C). In the mid- to late-2000s, the Bill and Melinda Gates Foundation funded at least two different global clinical trials for Truvada as a prevention measure against HIV. It gave more than \$13 million to the nonprofit, Family Health International, which oversaw the first trial (in sub-Saharan Africa) and provided more than \$15.7 million to the J. Gladstone Institutes which oversaw the second clinical trial, testing Truvada in patients from developed and developing countries.⁸⁷

c) The Role of AIDS Activists

Dr. Anthony Fauci (hereinafter “Fauci”) and other staff from these federal health agencies credit AIDS community activists with motivating government action on AIDS in the 1980s and 1990s, when widespread stigma and misunderstanding otherwise slowed government investment.⁸⁸ Activists like Larry Kramer, the most famous co-founder of AIDS Coalition to Unleash Power (“ACT UP”), repeatedly took to the press to criticize the U.S.

85. *Id.* at 25; see also WTO, *Compulsory licensing of pharmaceuticals and TRIPS*, TRIPS AND HEALTH: FREQUENTLY ASKED QUESTIONS, https://www.wto.org/english/tratop_e/trips_e/public_health_fa_q_e.htm (last visited Apr. 11, 2024) (providing WTO's definition of compulsory licensing).

86. See *Doha+10: More People Accessing HIV Treatment*, UNAIDS.ORG (Nov. 22, 2011), <https://www.unaids.org/en/resources/presscentre/featurestories/2011/november/20111123doha#:~:text=The%20Declaration%20clarified%20the%20scope,drugs%20for%20AIDS%2Drelated%20illnesses.>

87. See Peterson et al., *Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial*, 2 PLOS CLINICAL TRIALS 27 (2007) (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with FHI and Gates Foundation financial support); see also Robert M. Grant et al., *Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men*, 363 NEW ENG. J. MED. (27) 2587 (2010) (sharing the NIAID-led, Gates Foundation-supported, and Gilead-assisted iPrEx clinical Truvada for PrEP study results from men in Peru, Ecuador, Brazil, San Francisco, Boston, Thailand, and South Africa); *Committed Grants*, BILL & MELINDA GATES FOUND., <https://www.gatesfoundation.org/about/committed-grants> (last visited Mar. 11, 2023) (providing on downloadable spreadsheet the grant information for these two trials under grant opportunity codes OPP19789, OPP19789_01, and OPP48162).

88. See National Institutes of Health, *In Their Own Words... NIH Researchers Recall the Early Years of AIDS: Anthony S. Fauci, M.D. – Transcript of Interview 03* at 18–19, <https://history.nih.gov/display/history/Dr.+Anthony+S.+Fauci+Transcript?preview=/8881339/8881336/Fauci93.pdf> (last accessed Apr. 8, 2024).

government for its inaction.⁸⁹ Kramer and other ACT UP activists personally targeted leaders of federal agencies (such as by calling Fauci a “murderer”) in op-eds,⁹⁰ occupied the FDA campus,⁹¹ protested at the National Institutes of Health (NIH) campus,⁹² and in performed other political actions.⁹³ These efforts earned AIDS activists seats at the table with public and private institutions leading efforts to combat the virus. Fauci recalled that “a major part of [his] work in [the HIV/AIDS] epidemic [had] been opening the doors and breaking down the barriers between the activist groups and the scientific community . . . allow[ing] [them] to see the impact of the disease at the grassroots level . . . changing the way that [they] do business[.]”⁹⁴ In response to the AIDS activism, in 1992, the FDA created a new process for accelerated drug approval that lasts to this day.⁹⁵ This unlikely coalition of activists and institutions would work together in the 1990s and 2000s to develop highly active ARTs.⁹⁶

d) The Role of Universities

Universities performed much of the fundamental chemistry research necessary to develop AIDS treatments such as Truvada and lamivudine, a separate and competing NRTI therapy (discussed in “Emory Scientists Synthesize Emtricitabine and License it to Burroughs-Wellcome,” *infra*, Section III.B.2.a). The AIDS crisis began just as the effects of the Bayh-Dole Act of 1980 were being felt across American universities.⁹⁷ The Act enabled the modern transfer of technologies from university settings to startup and larger commercial enterprises through new incentives for university patent ownership.⁹⁸

89. See Kramer, *supra* note 49.

90. See Larry Kramer, *An Open Letter to Dr. Anthony Fauci*, SAN FRANCISCO EXAMINER (June 26, 1988), <https://aep.lib.rochester.edu/node/49111>.

91. See Douglas Crimp, *Before Occupy: How AIDS Activists Seized Control of the FDA in 1988*, ATLANTIC (Dec. 6, 2011), <https://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302/>.

92. See *ACT UP ACCOMPLISHMENTS—1987–2012*, ACT UP NY, <https://actupny.com/actions> (last accessed Apr. 8, 2024).

93. *Id.*

94. See *In Their Own Words*, *supra* note 88.

95. See *Understanding the History and Use of the Accelerated Approval Pathway*, AVALERE (Jan. 4, 2022), <https://avalere.com/insights/understanding-the-history-and-use-of-the-accelerated-approval-pathway>.

96. *Id.*

97. See *generally Bayh-Dole Act*, DREXEL UNIV. OFF. RSCH. & INNOVATION, <https://drexel.edu/research/innovation/technology-commercialization/bayh-dole-act/> (last visited Nov. 21, 2022).

98. See *id.*

e) The Role of Pharmaceutical Companies

Pharmaceutical companies of all sizes—from university-initiated startups to big pharma—began engaging in HIV/AIDS treatment development in the 1980s, beginning with pharmaceutical company Burroughs Wellcome’s AZT in 1987.⁹⁹ The company that would become leading antiviral manufacturer in the HIV/AIDS space as the maker of Truvada, Gilead Sciences, Inc., was only a brand-new small startup at the time.

The coalition to end HIV through increasingly effective treatments therefore has included a very wide swath of public and private actors, organizations, and institutions.

B. PHASE II—THE AIDS INNOVATION ECOSYSTEM YIELDS TWO PROMISING COMPOUNDS

Of the many ARTs targeting HIV, two are critical to the story of Truvada:¹⁰⁰ (1) tenofovir (trade name Viread); and (2) emtricitabine (originally trade-named Coviracil, now under the trade name Emtriva).¹⁰¹ The invention stories for these two compounds follow similar paths: (1) chemists at universities developed what would become life-saving compounds; (2) the chemists quickly published and patented their compounds for their ART activity; (3) the chemists licensed their patented compounds to small and large pharmaceutical companies for clinical development and regulatory approval; and (4) large pharmaceutical companies abandoned drug development licenses in the uncertain HIV market which allowed smaller pharmaceutical companies to step in and develop breakthrough ARTs.

1. *Viread: Tenofovir Disoproxil Fumarate (TDF)*

This Section will cover the invention of the first component of Truvada: tenofovir. In the mid-1980s, Czech chemist Dr. Antonín Holý (hereinafter, “Holý”) at the Czechoslovak Academy of Sciences in Prague achieved his dream of creating an effective antiviral compound when he developed with Belgian physician and biologist Dr. Eric De Clercq (hereinafter, “De Clercq”) the antiviral compound tenofovir.¹⁰² Although Holý initially intended

99. See Alice Park, *The Story Behind the First AIDS Drug*, TIME, <https://time.com/4705809/first-aids-drug-azt> (last visited Nov. 21, 2022).

100. U.S. Food & Drug Administration, *Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021752s000_TruvadaTOC.cfm (last visited Sept. 11, 2022).

101. ’397 Patent, *supra* note 2 (describing combination in the Abstract).

102. See Michal Hocek, *Prof. RNDr. Antonín Holý, DrSc., dr. b. c. mult. – 75th Birthday – Foreword*, COLLECTION CZECHOSLOVAK CHEM. COMM’NS (2011), http://cccc.uochb.cas.cz/virtual_issues/holy/foreword/ (last visited Nov. 23, 2022).

tenofovir as a herpes simplex virus therapeutic, Holý and De Clercq's invention of tenofovir successfully treated HIV infections.¹⁰³ A small biopharmaceutical startup called Gilead Sciences, Inc. ("Gilead") licensed tenofovir from Holý and De Clercq when they noticed the initial tenofovir license to a large pharmaceutical company lapsed (as discussed in Section III.B.1.b, *infra*). Gilead developed tenofovir into the clinically useful NtRTI for HIV treatment called tenofovir disoproxil fumarate.

a) Holý and De Clercq Synthesize TDF and License to Bristol-Myers

Holý was initially interested in building chemical analogues of the DNA and RNA building blocks, known as nucleotides (discussed in Section II.B, Antiretroviral Technology, *supra*), to inhibit transcription of herpes simplex virus (HSV) DNA into RNA in host human cells.¹⁰⁴ He found a research partner in Belgium, De Clercq, who was interested in clinically studying the antiviral effects of such compounds to treat infections and cancer.¹⁰⁵ In 1978, they succeeded by synthesizing their first antiviral compound, one active against HSV: dihydroxypropyladenine (DHPA).¹⁰⁶

In addition to HSV, the research team hypothesized their nucleoside analog technology could have antiviral activity against a wide range of viruses in humans and experimented with additional chemical modifications to DHPA. Holý and De Clercq produced three additional highly effective antiviral nucleoside analogs based by modifying DHPA: (1) cidofovir, used today to treat eye infections by cytomegalovirus in AIDS patients; (2) adefovir, used today to treat hepatitis B infection (HBV); and, perhaps most crucially, (3) tenofovir (9-(2-Phosphonyl-methoxypropyl)adenine (PMPA)¹⁰⁷), used today to treat HIV and/or HBV infections.¹⁰⁸ In 1985 and 1986, Holý submitted patent applications on these DHPA-derived nucleoside analogs,

103. *See id.*

104. *See id.*

105. *See id.*

106. *See id.*; see also Erik De Clercq et al., *(S)-9-(2,3-Dihydroxypropyl)adenine: An Aliphatic Nucleoside Analog with Broad-spectrum Antiviral Activity*, 200 SCI. 563, 563–65 (1978) (presenting De Clercq and Holý's first DHPA work).

107. *See, e.g.*, Steven G. Deeks et al., *Safety, Pharmacokinetics, and Antiretroviral Activity of Intravenous 9-[2-(R)-(Phosphonomethoxy)propyl]adenine, a Novel Anti-Human Immunodeficiency Virus (HIV) Therapy*, in *HIV-Infected Adults*, 42(9) ANTIMICROBIAL AGENTS & CHEMOTHERAPY 2380, 2380–84 (1998) (sharing Gilead's first human trials of PMPA later rebranded tenofovir, one of the two core drugs in Truvada).

108. *Id.*

which drew the attention of the global pharmaceutical industry.¹⁰⁹ The patents claimed compounds with broad activity against many viruses—including retroviruses—and were granted in the United States, which enabled a series of licensing deals for the technologies.¹¹⁰

Bristol-Myers was the first major pharmaceutical company to license the DHPA-derivatives from Holý and De Clercq and launched preclinical trials in 1987.¹¹¹ A clause in the license agreement contained an out for the researchers invested in the compounds' development into powerful treatments: "In the event development is discontinued, all rights must be returned to [the Czech Academy of Sciences] together with all materials, obtained results, and documentation."¹¹² When Squibb merged with Bristol-Myers to form Bristol-Myers Squibb in 1989, the new company cut development of the DHPA derivatives and other HIV antivirals.¹¹³ But their director of antiviral chemistry, John Martin, disagreed with the decision. He believed in the compounds' value as antiviral treatments, so when termination clause was triggered in 1990, Martin sought to continue the drugs' development elsewhere. Martin moved his team of scientists to the then-small biotechnology development company, Gilead Sciences, Inc.¹¹⁴

b) Beginnings of Gilead Sciences, Inc. and Its License for TDF Development

Doctor-turned-venture-capitalist Dr. Michael Riordan (hereinafter, "Riordan") founded Gilead in Foster City, California in 1987.¹¹⁵ Riordan's interest in developing antiviral treatments began with a personal experience with dengue fever—a mosquito-borne virus—that knocked him "flat on [his] back for three weeks" while on a Luce scholarship to East Asia working in a children's malnutrition clinic before beginning medical school.¹¹⁶ Prior to founding Gilead, Riordan earned degrees in biology, chemical engineering, medicine, and business and sought to use his training to build a world-leading

109. See *Antonín Holý 85 – Story of tenofovir*, INST. ORGANIC CHEMISTRY & BIOCHEMISTRY CZECH ACAD. SCIS. (Sept. 1, 2021), <https://www.uochb.cz/en/news/342/antonin-holy-85-story-of-tenofovir>.

110. See, e.g., U.S. Patent No. 4,808,716 (belonging to Czech Academy of Sciences and later Gilead Sciences, Inc. by assignment for synthesis of tenofovir compounds) (expired 2006) [hereinafter '716 Patent].

111. See *Antonín Holý 85 – Story of tenofovir*, *supra* note 109.

112. *Id.*

113. *Id.*

114. *Id.*

115. Kathryn S. Brown, *Balms from Gilead* at 31, 33, WASH. UNIVERSITY MAG. (1997), <https://riordangileadsciencesarticle.wordpress.com> (last visited Nov. 23, 2022).

116. See *id.*

antiviral therapy company.¹¹⁷ He did so by starting Gilead in the Bay Area with \$2 million in help from his Menlo Ventures venture capital firm partners¹¹⁸—one of whom, H. DuBose Montgomery, also was very frustrated by the lack of treatments available for the common cold while he had been experiencing a particularly bad one.¹¹⁹ Gilead initially focused on “antisense” oligonucleotide-based therapeutics, but upon recruiting Bristol-Myers’ Martin as Chief Scientist in 1990, the Gilead team refocused on candidates Martin viewed as most likely to succeed: the small molecule DHPA derivatives Martin started to develop at Bristol-Myers.¹²⁰ Gilead entered into license agreements with the Czech Academy of Sciences and began advancing all three DHPA derivatives as potential antiviral treatments in 1991–92.¹²¹

Gilead quickly embarked on preclinical trials of subcutaneous tenofovir to demonstrate the tenofovir compound’s effectiveness against HIV.¹²² Gilead partnered with nearby universities and hospitals—the University of Washington, the University of California, San Francisco, and San Francisco General Hospital—to study HIV in animals and in HIV/AIDS patients.¹²³ As intravenous injection of tenofovir into humans proceeded to human clinical trials,¹²⁴ Gilead worked to address challenges in formulating tenofovir in a more convenient oral form.

The two primary challenges Gilead faced in turning tenofovir into a practical oral HIV treatment were: (1) poor absorption of tenofovir by the digestive system; and, once absorbed, (2) poor transfer across cell membranes

117. *See id.*

118. *See id.*

119. *See The Golden Age of Antiviral Drugs*, FORBES (Oct. 27, 2003), <https://www.forbes.com/global/2003/1027/090.html?sh=caaa6d7753b3>.

120. *See* FORBES, *supra* note 119.

121. *Id.*; *see also* John C. Martin, *License Agreement – Gilead Sciences Inc., the Institute of Organic Chemistry and Biochemistry of the Academy of Sciences of the Czech Republic, and Rega Institute for Medical Research*, GILEAD SCIS., INC. (Dec. 27, 2000), <https://corporate.findlaw.com/contracts/operations/license-agreement-gilead-sciences-inc-the-institute-of.html>.

122. *See, e.g.*, Che-Chung Tsai et al., *Prevention of SIV Infection in Macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine*, 270 SCI. 1197 (1995) (describing the first simian trial coordinated by Gilead to demonstrate effectiveness of tenofovir against HIV infection or replication).

123. *See, e.g.*, Patricia Barditch-Crovo et al., *Phase I/II Trial of the Pharmacokinetics, Safety, and Antiretroviral Activity of Tenofovir Disoproxil Fumarate in Human Immunodeficiency Virus-Infected Adults*, 45 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1 (2001) (last visited Nov. 23, 2022) (including co-authors from San Francisco General Hospital, UCSF, and the University of Washington).

124. *See* Deeks et al., *supra* note 107.

into cells, where tenofovir is able to block viral replication.¹²⁵ Under Riordan and Martin, Gilead led development on chemical modifications to the tenofovir molecule to make a prodrug that improved cellular uptake for the first half of the 1990s.¹²⁶ Years of attempts by Gilead at oral prodrugs for tenofovir/PMPA yielded, in 1997, one lead compound out of eight prodrugs that had advanced to preclinical studies in dogs.¹²⁷ Initially called bis-POC PMPA, Gilead renamed the most effective prodrug to tenofovir disoproxil fumarate (TDF) during the subsequent human trials.¹²⁸ Immediately, Gilead patented many of the promising tenofovir prodrug compositions, including TDF, as well as their synthesis.¹²⁹

Gilead achieved a commercial breakthrough when the FDA approved TDF for adults (trade name Viread) in 2001, only six months after Gilead filed a New Drug Application under the FDA's accelerated approval pathway.¹³⁰ By this time, Riordan had retired from Gilead and placed the direction of the company in Martin's hands.¹³¹ Riordan saw the company grow from his initial idea to a biopharmaceutical company with a workforce of over 250 employees and a valuation of \$850 million by his 1997 retirement. Martin led Gilead until his retirement in 2019, and he grew the company into a large biopharmaceutical manufacturer with more than 10,000 employees and a valuation in the tens of billions of dollars.¹³²

Viread faced challenges upon FDA marketing approval. First, the FDA had concerns about effects on bone density and renal toxicity when it approved Viread in 2001 on a fast-track basis, conditioning the approval on continued clinical studies by Gilead to evaluate these side effects.¹³³ Second,

125. See Chanie Wassner et al., *A Review and Clinical Understanding of Tenofovir: Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide*, 19 J. INT'L ASS'N PROVIDERS AIDS CARE 1 (2020).

126. See Jeng-Pyng Shaw et al., *Metabolism and Pharmacokinetics of Novel Oral Prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in Dogs*, 14 PHARMACEUTICAL RSCH. 1824 (1997).

127. See *id.*

128. See Barditch-Crovo et al., *supra* note 123.

129. See, e.g., U.S. Patent No. 5,935,946 (granted to Gilead Sciences, Inc.; expired 2017).

130. See U.S. Food & Drug Admin., *Drug Approval Package: VIREAD® (Tenofovir Disoproxil Fumarate) Tablets* (Oct. 26, 2001), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-356_Viread.cfm#:~:text=Approval%20Date%3A%2010%2F26%2F01 (last visited Apr. 8, 2024).

131. See FORBES, *supra* note 119.

132. See *Gilead Sciences Inc: Overview*, GLOBALDATA.COM (2022), <https://www.globaldata.com/company-profile/gilead-sciences-inc/> (last visited Nov 23, 2022); see also Press Release, Gilead Scis., Inc., *Gilead Sciences Comments on the Passing of John C. Martin, PhD* (Mar. 31, 2021) (describing John Martin's legacy at Gilead).

133. See *Drug Approval Package: VIREAD®*, *supra* note 130.

the Doha Declaration issued that year empowered countries to issue compulsory licenses on drugs critical for public health like Viread; the Declaration therefore incentivized Gilead to launch a face-saving, proactive approach of *voluntary* licensing of TDF (and its future HIV ARTs) to governments in need internationally.¹³⁴ While several countries later threatened or demanded that Viread be licensed to them via compulsory licenses, this was very rare considering the global reach Viread had in treating HIV.¹³⁵ As borne out by Martin’s record of rapid growth at Gilead as its leader, the company was able to manage both of these challenges with TDF/Viread.¹³⁶

2. *Coviracil: Emtricitabine, Marketed Now as Emtriva*

While Holý and De Clercq initiated negotiations with Martin and Riordan for Gilead to license tenofovir in 1990, Emory University chemist Dr. Dennis Liotta (“Liotta”), a “serial entrepreneur,”¹³⁷ synthesized emtricitabine—the compound that would become the second component of Truvada. With a collaborative team including Liotta’s chemistry group at Emory, an Emory virologist (Dr. Raymond Schinazi, hereinafter “Schinazi”), and scientists at pharmaceutical companies of both large (Dr. George Painter, hereinafter “Painter,” and Dr. David Barry, hereinafter “Barry,” at Burroughs-Wellcome) and small (Dr. David Barry’s startup, Triangle Pharmaceuticals) sizes, emtricitabine entered clinical development into an ART against HIV.¹³⁸

a) Emory Scientists Synthesize Emtricitabine and License to Burroughs-Wellcome

Liotta’s motivation to pursue nucleoside analogs as antivirals began in 1989, when his collaborator Schinazi shared about an interesting conference poster he saw disclosing the synthesis of a new cytidine analog, later called 3TC, with “anti-HIV activity with no apparent cytotoxicity [toxicity to cells]”

134. See UNAIDS.ORG, *supra* note 86; see also THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (at approximately the 38-minute mark, containing Gilead executive vice president Gregg Alton’s explanation of Gilead’s extensive voluntary licensing system).

135. See, e.g., IHS Global Insight, *Indonesia Issues Compulsory Licenses Against Seven HIV, Hepatitis Drugs*, S&P GLOBAL MKT. ANALYSIS (Oct. 12, 2012), <https://www.spglobal.com/marketintelligence/en/mi/country-industry-forecasting.html?ID=1065972339>.

136. See GLOBALDATA.COM, *supra* note 132.

137. See Dr. Dennis Liotta, *About Dr. Dennis Liotta*, LIOTTA RSCH. GRP., <https://liottaresearch.org/> (last visited Nov. 24, 2022) (showing Liotta’s trademarked lab group logo and describing how Liotta “co-founded more than ten biotech companies” and sits on advisory boards for “more than a dozen biotech companies and venture capital firms.”).

138. See generally Dennis C. Liotta & George R. Painter, *Discovery and Development of the Anti-Human Immunodeficiency Virus Drug, Emtricitabine (Emtriva®)*, 49 ACCOUNTS CHEM. RSCH. 2091 (2016), (providing Liotta and Painter’s first-hand account of their research process and relevant anecdotes from their development of emtricitabine).

in cell-culture studies.¹³⁹ Liotta and Schinazi were aware of the toxicity problems of the early HIV nucleoside analog ARTs and agreed to work together at Emory to develop low-toxicity NRTIs.¹⁴⁰

Liotta first attempted to replicate the synthesis of the cytidine analog that Schinazi told him about. The published synthesis was “inefficient,” so he applied organic chemistry skills to develop a more efficient synthesis.¹⁴¹ Cytosine is a nucleobase and a portion of the nucleoside cytidine; cytosine alone lacks the ribose base that allows cytidine to be included in an RNA chain.¹⁴² Liotta’s synthesis resulted in a pair of analogs to cytidine that are mirror images of each other, referred to in organic chemistry as enantiomers.¹⁴³

Schinazi confirmed the anti-HIV activity and low-toxicity of Liotta’s racemic 3TC mixture and invited his long-standing collaborator Painter, a researcher at Burroughs-Wellcome interested in NRTI development, to verify the same.¹⁴⁴ This first low-toxicity cytosine analog, named by Liotta “3TC,” would quickly be developed as a component of other important HIV drugs, such as lamivudine.¹⁴⁵ As interest in cytosine analogs as anti-HIV therapeutics spread, Liotta and Schinazi competed with researchers at Yale, the University of Georgia, and pharmaceutical companies like GlaxoSmithKline (GSK) to isolate the (-) enantiomer from the more toxic (+) enantiomer efficiently. Simultaneously, Liotta had been working on syntheses for fluorinated versions of 3TC and found the resultant racemic mixture (“FTC”) *more* potent against HIV and HBV but similarly or *less* toxic than the original 3TC. Importantly, neither FTC enantiomer was more toxic than the other, though one enantiomer was “100 times more potent” than the other.¹⁴⁶ The “(-)”-coded enantiomer of “FTC” became known as emtricitabine.¹⁴⁷ Liotta and his

139. *Id.* at 2091–92; *see also* Théo Bourgeron & Susi Geiger, *(De-)assetizing Pharmaceutical Patents: Patent Contestations Behind a Blockbuster Drug*, 51 *ECON. & SOC’Y* 23, 30–31 (2021) (“In 1989 . . . Schinazi learned of an interesting new compound, called 3TC, being developed by Canadian biotech firm, BioChem Pharmaceuticals.”).

140. *See* Liotta & Painter, *supra* note 138, at 2092 (“Given the side effect profiles of the approved NRTIs and the rapid development of resistance to them . . . it was clear that additional drugs were needed.”).

141. *Id.*

142. *See* Lee W. Janson & Marc E. Tischler, *Nucleosides, Nucleotides, DNA, and RNA*, in *THE BIG PICTURE: MEDICAL BIOCHEMISTRY* (2018).

143. *See* Liotta & Painter, *supra* note 138, at 2092–94. In organic chemistry, enantiomers are a set of two molecules that are mirror images of each other in 3D space. As a result, isolating the two from each other may show each has slightly different chemical activity. *See id.* at 2093.

144. *See id.* at 2093.

145. *Id.*

146. *Id.* at 2094.

147. *Id.* at 2092.

assignee Emory filed a patent application for emtricitabine in 1991 and the PTO granted it in 1995.¹⁴⁸ The Canadian scientist's company whose work inspired Liotta and Schinazi challenged in district court Liotta's equitable conduct when prosecuting the patent before the U.S. Patent and Trademark Office (USPTO) given the inspiration. After years of litigation, Liotta and colleagues retained the rights to their FTC patent.¹⁴⁹

Before that inventorship and novelty dispute, Burroughs-Wellcome licensed emtricitabine from Emory to conduct the requisite preclinical studies for an Investigational New Drug Application (IND) with the FDA.¹⁵⁰ Ahead of filing their IND that year, Glaxo offered to purchase Burroughs-Wellcome and the two ultimately merged into one entity, Glaxo-Wellcome.¹⁵¹ Glaxo-Wellcome decided to abandon the emtricitabine IND and prioritize 3TC development because the 3TC candidate was ahead of FTC in the FDA approval process.¹⁵²

b) Barry Leaves Big Pharma to Develop Emtricitabine with His Own Company, Triangle

Dr. David Barry (hereinafter, "Barry") was a scientific leader of Burroughs-Wellcome's antiviral development team when it found and commercialized AZT in 1987.¹⁵³ In 1995, Barry was the head of HIV treatment discovery and development at Burroughs-Wellcome.¹⁵⁴ Barry eventually left Glaxo-Wellcome in 1996 to form his own company which would restart development of emtricitabine in collaboration with Liotta.¹⁵⁵ Like Holy's initial license to develop tenofovir with Bristol-Myers (discussed in Section III.B.1: Viread, *supra*), Liotta's initial license to develop emtricitabine to Burroughs-Wellcome (and later Glaxo-Wellcome) terminated if the company shelved the project.¹⁵⁶ Barry used this termination clause to his advantage. In 1996, he formed Triangle Pharmaceuticals, Inc. in Durham, North Carolina, and Triangle

148. *See generally* U.S. Patent No. 5,210,085 (filed (expired 2010) (claiming initial FTC compound and initial uses) [hereinafter '085 Patent].

149. *See generally* Emory Univ. v. Glaxo Wellcome Inc., No. 1:96-CV-1868-GET, 1997 WL 817342 (N.D. Ga. July 14, 1997) (denying Glaxo's motion for summary judgment to invalidate Liotta's and Emory's 3TC patent); *see also Emory Case Study: Dispute Details – Awards/Legal Rulings*, IPADVOCATE, <http://ipadvocatefoundation.org/studies/emory/8.cfm> (last visited Mar. 12, 2023).

150. *See* Liotta & Painter, *supra* note 138, at 2095.

151. *Id.*

152. *Id.*

153. *See id.*

154. *See id.*

155. *Id.*

156. *See id.*

licensed Emory's emtricitabine IP to develop the drug into a commercial product.¹⁵⁷

Triangle eagerly picked up emtricitabine development where Burroughs-Wellcome left off. Triangle leveraged the earlier preclinical data supporting emtricitabine to submit a renewed IND in 1997 and, given emtricitabine's potential for once-daily dosing and promising early trials, the FDA granted it "Fast Track" status in 1998.¹⁵⁸ In the same period, Barry successfully took Triangle public.¹⁵⁹ Over the next four years, clinical trials would show emtricitabine reduced HIV viral load more than the already-marketed 3TC products; Triangle submitted a New Drug Application (NDA) to the FDA in 2002 based on this data, under the trade name Coviracil.¹⁶⁰ During that time, Emory sued Glaxo-Wellcome and Biochem Pharma for infringement of Emory's 3TC patents and, separately, sued the same defendants to claim Emory's patent inventorship and ownership of emtricitabine; the eventual settlements gave Emory both cash and a license to the patent rights to emtricitabine, while Glaxo-Wellcome's successor GlaxoSmithKline received a license to 3TC.¹⁶¹ With this settlement in 2002, regulatory approval and commercialization of emtricitabine became unencumbered by patent litigation.

Unexpectedly, Barry died while travelling for business in January 2002, only months before Triangle submitted the full emtricitabine NDA to the FDA.¹⁶² News of his death rocked the small company, the Research Triangle (the Raleigh-Durham-Cary tri-city region in North Carolina), the AIDS innovation community he helped lead, and the pharmaceutical industry. Though another Triangle officer took on his role, a power vacuum formed at Triangle without its founder-leader and its high-potential anti-HIV & anti-HBV emtricitabine made it an attractive candidate for acquisition.¹⁶³

C. PHASE III—TRUVADA AS THE LEADING METHOD OF HIV TREATMENT AND PREVENTION

Gilead Sciences, Inc. moved aggressively after FDA approval of Viread to create what would become one of the best-selling HIV drugs, Truvada.

157. *Id.*

158. *Id.*

159. See Yale Class of 1965, *David Walter Barry*, YALE CLASS 1965: LUX ET VERITAS, <https://yale1965.org/david-walter-barry/> (last visited Nov. 24, 2022).

160. See Liotta & Painter, *supra* note 138, at 2096.

161. *Id.*

162. See Yale Class of 1965, *supra* note 159.

163. See Rick Smith, *The sad saga of David Barry, Triangle Pharmaceuticals nears a close*, WRAL TECHWIRE (June 25, 2010), <https://wraltechwire.com/2010/06/25/the-sad-saga-of-david-barry-triangle-pharmaceuticals-nears-a-close/>.

Between 2002 and 2005, Gilead acquired the intellectual property rights to emtricitabine by acquiring Triangle and purchasing Emory's patent rights in exchange for a hefty sum. By 2004, Gilead had secured FDA approval of both Emtriva (formerly Coviracil) and a combination ART, a co-formulation of emtricitabine and TDF: Truvada. Truvada quickly dominated the HIV treatment market. Public health administrations adapted their existing Truvada clinical trials to methods of HIV *prevention*. The CDC eventually patented a new method of treatment with Truvada for Pre-Exposure Prophylaxis (PrEP). An unprecedented patent litigation over the rights to PrEP reasonable royalties between the U.S. government and Gilead ensued in 2019; meanwhile, millions of Americans received Truvada to prevent or treat HIV infection.¹⁶⁴

1. *Method One: Combining TDF with Emtricitabine for HIV Treatment as Truvada*

Truvada, more potent and safer than previous treatments, came to dominate the HIV ART market due to aggressive strategies by Gilead. Gilead committed fully to the second active ingredient of Truvada, emtricitabine, by acquiring (as opposed to licensing) relevant intellectual property and existing clinical operations. Gilead then used its regulatory expertise and approved one-component drugs, Viread and Emtriva, to receive accelerated approval for Truvada as bioequivalent to Viread and Emtriva. Gilead turned into the behemoth pharma company it is known for today largely thanks to this success.

a) Gilead Purchases Triangle for Emtricitabine

In 2002, Gilead was riding the newfound commercial success of tenofovir (Viread).¹⁶⁵ But, Gilead's leaders observed doctors would commonly prescribe many different ARTs at once to avoid the kind of viral resistance and HIV rebound first encountered by HIV/AIDS patients on AZT alone in the late

164. *See, e.g.*, United States v. Gilead Scis., Inc., 515 F. Supp. 3d 241, 244 (D. Del. 2021) (denying Government's motion to strike affirmative defenses and dismiss Gilead's counterclaims of non-infringement & invalidity in Government's patent infringement suit against Gilead regarding Gilead's marketing of Truvada for PrEP); *see also* The Editorial Board, *Gilead Sciences Defeats the CDC*, WALL ST. J. (May 10, 2023), <https://www.wsj.com/articles/cdc-federal-jury-gilead-sciences-truvada-patent-4ae9fa8e> (sharing the jury verdict of noninfringement and CDC patent invalidity).

165. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (discussing Truvada's initial successes at approximately the 20-minute mark, 38-minute mark, and 50-minute mark).

1980s and early 1990s.¹⁶⁶ Many criticized this practice as wasteful and risky, since no clinical studies tested combinations of treatments.¹⁶⁷

Gilead's leaders thought they should make a single product doctors could prescribe for an HIV patient to achieve and safely maintain "undetectable" status for their lifetime.¹⁶⁸ It struck the leaders of Gilead that there was an enormous opportunity for such a drug to succeed. Gilead held regular meetings with HIV/AIDS patients and AIDS community activists. What struck Gilead scientists the most was how any meeting spanning the hours of 4:00 AM or PM, 8:00 AM or PM, or 12:00 AM or PM would involve the crowd of AIDS patients having alarms go off to take their once-every-four-hours set of medications.¹⁶⁹

For Gilead, the opportunity presented by Triangle and its emtricitabine product was too good to pass over. Emtricitabine had negligible toxicity to cells,¹⁷⁰ while Gilead's TDF presented known toxicities to bone density and kidney systems in humans.¹⁷¹ Thus, emtricitabine was advantageous over many other NtRTIs (as well as NRTIs) as a candidate to combine with TDF for a combination treatment to address viral resistance and HIV rebound concerns. Emtricitabine and the tenofovir in TDF both inhibit the replication action of the same HIV enzyme, but in two different ways (as cytidine and adenosine imitators, respectively). Gilead scientists hypothesized their combination should have a strong clinical synergistic effect of HIV inhibition.¹⁷² Emtricitabine was a new potent NRTI product expected to enter the market in the next year with lesser-known branding (in its trademark, Coviracil, and manufacturer, Triangle).¹⁷³ Triangle had just suffered the tragic loss of its visionary leader, leaving the Triangle team open to new leadership through a merger or acquisition.¹⁷⁴

On December 4, 2002, Gilead and Triangle announced a "definitive agreement" for Gilead to purchase Triangle via a two-step tender offer.¹⁷⁵

166. *See id.*

167. *See* Alice Tseng et al., *The Evolution of Three Decades of Antiretroviral Therapy: Challenges, Triumphs and the Promise of the Future*, 79 BRIT. J. CLINICAL PHARMACOLOGY 182, 182–94 (2015).

168. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (containing clip of Norbert Bischofberger, EVP of R&D at Gilead Sciences, sharing motivations and goals for Atripla and Truvada for HIV treatment at the 20-minute mark).

169. *Id.*

170. *See* Liotta & Painter, *supra* note 138, at 2094.

171. *See* *Drug Approval Package: VIREAD®*, *supra* note 130.

172. *See supra* Section II.B.

173. *See* Liotta & Painter, *supra* note 138.

174. *See* Smith, *supra* note 163.

175. *See* Gregg Alton, *Schedule TO-C Triangle Pharmaceuticals Inc.: Tender Offer Statement under Section 14(d)(1) or 13(e)(1) of the Securities Exchange Act of 1934*, GILEAD SCIS., INC., SECURITIES

Gilead purchased Triangle, including its intellectual property portfolio and North Carolina headquarters, for \$464 million.¹⁷⁶ As a part of the emtricitabine purchase, Gilead took the unusual step of purchasing the full patent rights to emtricitabine from their original owners, Emory University, for a single payment of \$525 million, instead of maintaining a license with Emory.¹⁷⁷ Gilead made clear its primary intention in acquiring Triangle in its 2002 announcement: Gilead intended to both commercially launch the delayed Coviracil and build a combination therapy of Viread and Coviracil.¹⁷⁸

b) Gilead Seeks Accelerated Approval for Anti-HIV Combination Therapy Truvada

Gilead quickly worked with worldwide health agencies to launch both an emtricitabine-only HIV treatment and a combination treatment of emtricitabine-tenofovir.¹⁷⁹ To gain more rapid approval for the combination therapy, Gilead pursued a clinical study route acceptable to American and European regulators for combination therapies of existing drugs: a single “bioequivalence” study, in lieu of the standard phases I through III of clinical trials for novel medicines.¹⁸⁰ Further, the American AIDS health agencies were excited and confident about the potential of this combination therapy and organized trials of their own with Gilead’s supporting input before FDA approval of the combination therapy.¹⁸¹

In March 2004, only eight months after emtricitabine was approved by the FDA, Gilead filed a New Drug Application for the combination anti-HIV

EXCHANGE COMMISSION (Dec. 4, 2002), <https://www.sec.gov/Archives/edgar/data/882095/000104746902005573/a2095407zsccto-c.htm> (last visited Nov. 24, 2022).

176. *See id.*

177. *See* Press Release, Emory Univ., Gilead Sciences and Royalty Pharma Announce \$525 Million Agreement with Emory University To Purchase Royalty Interest for Emtricitabine, (July 18, 2005), <https://www.emory.edu/news/Releases/emtri>.

178. *See* Alton, *supra* note 175.

179. In 2003, Gilead updated the NDA for Coviracil to reflect a replacement trade name: Emtriva. *See* U.S. Food & Drug Admin., *Drug Approval Package: Emtriva® (emtricitabine) 200 mg Tablets*, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021500_emtriva_toc.cfm#:~:text=Approval%20Date%3A%2007%2F02%2F2003 (last visited Nov. 24, 2022). The FDA granted approval for Emtriva that same summer; *Id.*

180. *See id.* (containing clinical trial basis in the Clinical Pharmacology and Biopharmaceutics Review report); *see also* European Medicines Agency, *Scientific Discussion: Truvada®*, MINN-Emtricitabine/Tenofovir disoproxil fumarate, https://www.ema.europa.eu/en/documents/scientific-discussion/Truvada-epar-scientific-discussion_en.pdf (last visited Nov. 25, 2022).

181. *See* National Institute of Allergy and Infectious Diseases (NIAID), *Safety of Tenofovir Disoproxil Fumarate (TDF) and Emtricitabine/TDF in HIV Infected Pregnant Women and Their Infants*, U.S. NAT’L LIB. MED.: CLINICALTRIALS.GOV (2004), <https://clinicaltrials.gov/ct2/show/NCT00076791> (last visited Nov. 25, 2022).

therapy of emtricitabine and TDF under the trade name Truvada.¹⁸² Gilead also filed the first patent, followed by several continuation applications, on daily treatment of HIV with 500 milligrams of Truvada that year.¹⁸³ Gilead would go on to receive three additional patents on treatment of HIV with Truvada, each with a terminal disclaimer to the first patent; all four patents have been listed in the FDA Orange Book drug patent listings for Truvada.¹⁸⁴

The AIDS innovation and regulation ecosystem was eager to deploy the new Truvada. Only five months later, in August, the FDA would approve Truvada for HIV treatment;¹⁸⁵ however, the FDA approved it conditionally based on Gilead's continued study of the toxicity and efficacy of Viread, especially related to the drug's renal effects.¹⁸⁶ In February 2005, the European Commission approved Truvada for HIV treatment too.¹⁸⁷ In October that year, Gilead announced its year-over-year third quarter revenue increased by 51%, with a record product sales of \$467.2 million during the third quarter of 2005 "driven primarily by Gilead's HIV product franchise, including the continued strong uptake of Truvada® . . . since its U.S. launch in August of 2004."¹⁸⁸

However, Gilead and the AIDS innovation ecosystem collaborating with it had even higher aims for Truvada. Gilead sought to combine Truvada with yet a third anti-HIV compound to treat the most severe HIV infections with a

182. See *Drug Approval Package: Truvada®*, *supra* note 30 (containing timeline of application and approval on page 1 of the linked Approval Letter).

183. See '397 Patent, *supra* note 2, at 1 (showing discrepancy between filing date of granted patent with first application on page 1).

184. See *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations – Patent and Exclusivity for: N021752*, FDA, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=021752&Appl_type=N (last visited Mar. 12, 2023) (listing Gilead's four patents on the 500 mg dose of Truvada set to expire in 2024).

185. *Id.*; see also 21 C.F.R. § 314.510 (defining process for FDA to grant marketing approval for a new drug based on a "surrogate endpoint that is reasonably likely" based on past evidence, in the Truvada case on evidence from FTC & TDF's independent trials, with the condition to continue clinical studies for verification post-marketing).

186. See *Drug Approval Package: Truvada®*, *supra* note 30 (containing post-marketing conditions of approval on pages 2–4 of the linked Approval Letter).

187. Press Release, Gilead Scis., Inc. European Commission Approves Truvada®, a Once-a-Day Tablet Containing Gilead Sciences' Anti-HIV Drugs Emtriva® and Viread® (Feb. 23, 2005), <https://www.gilead.com/news-and-press/press-room/press-releases/2005/2/european-commission-approves-truvada-a-onceaday-tablet-containing-gilead-sciences-antihiv-drugs-emtriva-and-viread>.

188. Press Release, Gilead Scis., Inc., Gilead Sciences Announces Third Quarter 2005 Financial Results (Oct. 18, 2005), <https://www.gilead.com/news-and-press/press-room/press-releases/2005/10/gilead-sciences-announces-third-quarter-2005-financial-results>.

once-daily pill.¹⁸⁹ Gilead ultimately succeeded in doing so in partnership with Bristol-Myers Squibb by making the product Atripla.¹⁹⁰ The U.S. Public Health Service recommended Truvada for post-exposure prophylaxis (post-HIV-exposure emergency treatment to reduce the risk of infection).¹⁹¹ Audaciously, many of the AIDS institutions partnered with Gilead to embark on a promising, entirely new area of tackling the HIV pandemic: prevention of HIV infection.

2. *Method Two: TDF with Emtricitabine as Truvada for PrEP Preventing HIV Infection*

Public health authorities, as discussed in this Section, were leading global trials on methods to prevent HIV infection from the late 1990s into the late 2000s, especially through continuous use of ART in HIV-negative but vulnerable populations. When Truvada was first approved for HIV treatment in 2004, the public health authorities leading the prevention clinical trials noticed the new drug's potential as a preventive. After clinical trials with other ARTs, including tenofovir alone, failed to show a PrEP regimen could work, public health authorities turned to Truvada. The CDC accessed Truvada with a Material Transfer Agreement (MTA) with Gilead, but the trials were funded by taxpayers and philanthropies. Finding success, the CDC patented Truvada for PrEP as a method of treatment to prevent HIV infection. After Gilead received FDA approval for the second indication of Truvada as Truvada for PrEP, access to the medicine by vulnerable populations has been limited. AIDS activists successfully pushed the U.S. government to enforce its patents against Gilead, though the government in 2023 lost a jury trial in its unprecedented patent litigation. There, the government had sought resource concessions from Gilead—in the form of one billion dollars in royalties—to help fund increased public assistance for the still-suffering HIV/AIDS community.¹⁹²

189. See THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (discussing Gilead's goals for Truvada at the 20, 38, and 54 minute marks).

190. See *id.*

191. See Adelisa L. Panlilio et al., *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*, NAT'L CTR. FOR INFECTIOUS DISEASES, CDC (Sept. 30, 2005), <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm>.

192. See Christopher Yasiejko & Michael Shapiro, *Gilead Beats US in Billion-Dollar Trial on Anti-HIV Patents (1)*, BLOOMBERG LAW (May 9, 2023), <https://news.bloomberglaw.com/ip-law/gilead-beats-us-in-billion-dollar-trial-on-anti-hiv-patents>; see also Press Release, Statement from Prep4All and PIPLI on the Disappointing Verdict in US v. Gilead, PREP4ALL (May 17, 2023), <https://prep4all.org/statement-from-prep4all-and-pipli-on-the-disappointing-verdict-in-us-v-gilead/> (“If the government prevails and obtains a royalty from Gilead, the proceeds

a) Breakthrough: Government, Philanthropy, Big Pharma Clinical Trials

At the time of the Truvada launch for HIV treatment in 2004, the HIV/AIDS innovation coalition leaders were starting to think seriously about the concept of PrEP for prevention of HIV infection in at-risk populations.¹⁹³ The CDC's first PrEP investigation using only tenofovir compounds in an animal trial in 1995 produced mixed results.¹⁹⁴ Though veteran clinical leaders that had been in the fight against AIDS since the 1980s openly questioned if PrEP was a high-value strategy to contain the lasting HIV pandemic,¹⁹⁵ interest in trying to develop PrEP again surged after the Viread approval. In 2004, at least six trials were planned to evaluate PrEP against HIV infection around the globe, though initially only through use of TDF (Viread).¹⁹⁶ One of the largest Viread for PrEP trials ongoing at the time was a study in Botswana coordinated by two of the world's largest global health philanthropies (the Bill & Melinda Gates Foundation as sponsors and Family Health International (FHI), in collaboration with Gilead for materials).¹⁹⁷ However, that trial would also fail to find clinically significant HIV protection from Viread alone.¹⁹⁸

could provide badly-needed funding to expand access to PrEP, HIV testing, and related care.”).

193. See Greg Szekeres et al., *Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians*, CTR. FOR HIV IDENTIFICATION, PREVENTION, & TREATMENT SERVS. (2004), http://www.uclaisap.org/documents/PreP_Report_FINAL_11_1_04.pdf (last visited Nov. 25, 2022).

194. Che-Chung Tsai et al., *Prevention of SIV Infection in Macaques by (R)-9-(2-phosphobonylmethoxypropyl)adenine*, 270 SCI. 1197, 1199 (1995); see also Leigh Peterson et al., *Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial*, 2 PLOS CLINICAL TRIALS 27 (2007) (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with Gates Foundation financial support).

195. See *The Evolution of HIV/AIDS Therapies*, CHEMICAL HERITAGE FOUND. & SCI. HIST. INST. (2012), <https://vimeo.com/59281508> (containing clip of at the minute mark Norbert Bischofberger, EVP of R&D at Gilead Sciences, and Dr. Paul Volberding of UCSF discussing the relatively low value of PrEP to containing the pandemic with its simultaneous importance to high-risk individuals' ability to protect themselves).

196. See Szekeres et al., *supra* note 193.

197. See Press Release, Bill & Melinda Gates Found., Family Health International Receives Grant to Evaluate Once-Daily Antiretroviral as a Potential Method of HIV Prevention, <https://www.gatesfoundation.org/ideas/media-center/press-releases/2002/10/family-health-international-receives-grant> (last visited Apr. 8, 2024); see also Peterson et al., *supra* note 194 (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with Gates Foundation financial support).

198. See Peterson et al., *supra* note 194 (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with Gates Foundation financial support).

In 2004, the CDC was interested in exploring combination ARTs as PrEP candidates and reached out to Gilead for its emtricitabine and tenofovir materials as well as basic guidance. The CDC signed a MTA with Gilead to enable the CDC to complete a study of emtricitabine and tenofovir as PrEP against HIV in animals.¹⁹⁹ The CDC's trial of Truvada for PrEP against HIV infection ("Truvada for PrEP"), the first of many Truvada for PrEP studies funded primarily by U.S. taxpayers through NIH grants, was very successful.²⁰⁰ Contrary to the terms of the CDC's MTA with Gilead, which stipulated neither party could file for patents arising from the resulting CDC trial, CDC scientists—possibly unaware of that clause—began filing method of treatment patents on Truvada for PrEP in 2006.²⁰¹ The CDC alerted Gilead to the trial's success, but made minimal mention of the patent filings or otherwise decided not to pursue enforcement of them for more than a decade;²⁰² instead, the CDC encouraged Gilead and other organizations starting to run or running tenofovir-as-PrEP clinical trials globally to shift to clinical trials of Truvada for PrEP in the late 2000s.²⁰³

The Bay Area hub of the broader AIDS innovation coalition led the way again (this time in regards to PrEP) with Dr. Robert Grant at UCSF spearheading the largest Truvada for PrEP study, dubbed the "iPrEx" study, beginning in 2006–07.²⁰⁴ Grant's study, which included observing almost 2500 men across seven distinct locations across the globe for three years, was supported by \$50 million in federal grants from the NIH and \$17 million in additional funding from the Bill & Melinda Gates Foundation, with minimal

199. See *Gilead Scis., Inc. v. United States*, 155 Fed. Cl. 336, 339 (2021).

200. See J. Gerardo García-Lerma et al., *Prevention of Rectal SHIV Transmission in Macaques by Daily or Intermittent Prophylaxis with Emtricitabine and Tenofovir*, 5 PLOS MED. 28 (2008) (finding statistically significant protection with combination therapy of tenofovir and emtricitabine, forming basis of CDC inventorship claim to Truvada as HIV PrEP).

201. See, e.g., U.S. Patent No. 9,044,509 (granted June 2, 2015) (claiming tenofovir disoproxil fumarate + emtricitabine as a method of treatment for prevention of HIV infection based on simian trials) [hereinafter '509 Patent].

202. See *Gilead Scis.*, 155 Fed. Cl. at 340.

203. See, e.g., Press Release, Ctrs. for Disease Control & Prevention, CDC Trial and Another Major Study Find PrEP Can Reduce Risk of HIV Infection among Heterosexuals, <https://www.cdc.gov/nchhstp/newsroom/2011/prepheterosexuals.html> (last visited Sep. 11, 2022) (sharing another PrEP study that the CDC supported after its initial agreement with Gilead).

204. See Robert M. Grant et al., *Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men*, 363 NEW ENG. J. MED. 2587 (2010) (sharing the NIAID-led, Gates Foundation-supported, and Gilead-assisted iPrEx clinical Truvada for PrEP study results from men in Peru, Ecuador, Brazil, San Francisco, Boston, Thailand, and South Africa).

materials support from Gilead.²⁰⁵ The study found that Truvada for PrEP reduced the risk of transmission of HIV to those following the regimen by as much as 92%.²⁰⁶ The wild success of the clinical trial prompted a call from President Obama in November 2010 to congratulate Grant and the rest of the NIH team for the remarkable findings.²⁰⁷

During this time, Gilead was simultaneously fighting a smear campaign by many AIDS activists against PrEP. At FDA hearings about the potential new Truvada for PrEP indication, the AIDS Healthcare Foundation, which represents AIDS care providers and patients globally, protested loudly: that the drug had problematic side effects and costs to patients; that the PrEP approach would incentivize unsafe sex despite continued circulation of other STIs; and that irregular adherence to the daily PrEP regimen would lead to Truvada-resistant HIV strains.²⁰⁸ Gilead did not fund, but only gave requested materials, for the leading trials that found Truvada to be effective as PrEP; in fact, Gilead was initially hesitant to pursue PrEP development, given its close collaboration in its HIV therapies with AIDS activists that disagreed with the concept, but the public health authorities pushed for Truvada to be made available as a preventive.²⁰⁹

b) Gilead Obtains FDA Approval and Markets Truvada for PrEP

The clear results of the iPrEx study in 2010, in addition to the similarly-successful “Partners PrEP” study (lead by AIDS coalition members the CDC and the University of Washington and with Gates Foundation financial support),²¹⁰ prompted Gilead to begin the development necessary to file a supplementary New Drug Application (sNDA) and new trade name for a second FDA-approved indication of Truvada: Truvada for PrEP.²¹¹ Gilead filed its sNDA for Truvada for PrEP in December 2012, relying on the two

205. Liz Highleyman, *CDC Has Patents on PrEP, Advocates Find*, POZ (Mar. 28, 2019), <https://www.poz.com/article/cdc-patent-prep-advocates-find>.

206. See Grant et al., *supra* note 204, at 2597.

207. See Christopher Glazek, *Why Is No One on The First Treatment to Prevent H.I.V.?*, NEW YORKER: ANNALS TECH. (Sept. 13, 2013), <https://www.newyorker.com/tech/annals-of-technology/why-is-no-one-on-the-first-treatment-to-prevent-h-i-v>.

208. See *id.*

209. See *id.*

210. See Jared M. Baeten et al., *Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women*, 367 NEW ENG. J. MED. 399 (2012) (sharing results of the Partners PrEP study evaluating Truvada for use in serodiscordant partners).

211. See Press Release, Gilead Scis., Inc., Gilead Sciences Submits Supplemental New Drug Application to U.S. Food and Drug Administration for Truvada® for Reducing the Risk of Acquiring HIV (Dec. 15, 2011), <https://www.gilead.com/news-and-press/press-room/press-releases/2011/12/gilead-sciences-submits-supplemental-new-drug-application-to-us-food-and-drug-administration-for-Truvada-for-reducing-the-risk-of-acquiring-hiv>.

studies supported by the Gates Foundation and other members of the AIDS innovation coalition.²¹²

Eight months later, in July 2012, Gilead secured FDA approval for the second indication for Truvada: Truvada for PrEP against HIV.²¹³ Though Grant had expected “a stampede” of demand for the drug to be prescribed as PrEP, even pre-approval, the controversy regarding PrEP’s adoption (discussed in Section III.C.2.a, *infra*) slowed the uptake of Truvada for PrEP. In 2013, a year after FDA approval, only a few thousand Americans were taking Truvada for PrEP, despite “at least half a million Americans” being good candidates due to their risk profiles.²¹⁴

Gilead predicted in 2013 that it would take five to ten years for PrEP to become more widely accepted and used in communities vulnerable to HIV’s spread.²¹⁵ Over the next seven years, profits for Truvada increased by billions of dollars as uptake of Truvada for PrEP gradually increased; however, the number of HIV infections annually would hold steady at about 40,000 per year.²¹⁶

c) United States Enforces PrEP Patents Against Manufacturer
Gilead

Carrying on the tradition of driving access to HIV/AIDS medicines, AIDS activists uncovered the CDC’s patents on Truvada for PrEP in 2018 and pushed for the CDC to take enforcement action.²¹⁷ James Krellenstein, co-founder of a modern AIDS activism organization called PrEP4All Collaboration, claimed “[t]he CDC has all these patents and is allowing Gilead to rip off the American people at the expense of public health.”²¹⁸ The modern AIDS activists asked the CDC to enforce its patents on Truvada for PrEP to

212. *See id.*

213. Press Release, Gilead Scis., Inc., U.S. Food and Drug Administration Approves Gilead’s Truvada® for Reducing the Risk of Acquiring HIV (July 16, 2012), <https://www.gilead.com/news-and-press/press-room/press-releases/2012/7/us-food-and-drug-administration-approves-gileads-Truvada-for-reducing-the-risk-of-acquiring-hiv>.

214. *See* Glazek, *supra* note 207.

215. *See id.*

216. *See* Christopher Rowland, *An HIV Treatment Cost Taxpayers Millions. The Government Patented It. But a Pharma Giant Is Making Billions*, WASH. POST (Mar. 26, 2019), https://www.washingtonpost.com/business/economy/pharma-giant-profits-from-hiv-treatment-funded-by-taxpayers-and-patented-by-the-government/2019/03/26/cee5afb4-40fc-11e9-9361-301ffb5bd5e6_story.html.

217. *See id.*

218. *Id.*

help the CDC fund Medicaid-based PrEP education and heavily-discounted PrEP distribution programs.²¹⁹

Reports on the AIDS activists' calls for action spurred a congressional hearing on May 16th, 2019, where the House Committee on Oversight and Government Reform called the Gilead CEO Daniel O'Day, Grant, and HIV/AIDS activists to testify.²²⁰ For hours, House Representatives interrogated the panel about the pricing of Truvada and the taxpayer funds that went into Grant's studies in relation to the CDC's patents.²²¹ Representative Alexandria Ocasio-Cortez, who had pushed the Committee to hold the hearing, entered into the congressional record a Yale Law report asserting the validity and enforceability of the CDC's patents. Through her questions, she began to make the case that the patents should be enforced against Gilead so that the government could seek lower-price guarantees or more need-based access programs from the manufacturer.²²² After the hearing, Committee Chair Elijah E. Cummings and Representative Ocasio-Cortez wrote to the Department of Health and Human Services Secretary Alex Azar requesting more information about the CDC's patents.²²³ In November, the U.S. Department of Justice Civil Division on behalf of the Department of Health and Human Services took the unprecedented step of bringing suit against its longtime AIDS innovation partner, Gilead, for willful infringement of the four CDC patents.²²⁴

Gilead vigorously defended the patent infringement claims—including seeking (to no avail) Patent Trial and Appeal Board *inter partes* review of the patents.²²⁵ In 2021, Gilead countersued for breach of contract regarding the CDC's PrEP patents arguing the CDC violated the terms in the CDC-Gilead Material Transfer Agreement that stipulated the CDC could not seek patents

219. *Id.*

220. See Press Release, House Committee on Oversight & Accountability, Committee to Hold Hearing on Gilead's Exorbitant Price for HIV Prevention Drug (May 14, 2019), <https://oversightdemocrats.house.gov/news/press-releases/committee-to-hold-hearing-on-gilead-s-exorbitant-price-for-hiv-prevention-drug>.

221. *Id.*

222. See *HIV Prevention Drug: Billions in Corporate Profits after Millions in Taxpayer Investments: Hearing Before the Committee on Oversight and Reform*, 116 Cong. 14-16 (May 16, 2019), <https://docs.house.gov/meetings/GO/GO00/20190516/109486/HHRG-116-GO00-Transcript-20190516.pdf>.

223. Eric Sagonowsky, *Lawmakers Clash as Gilead CEO Takes Congressional Hot Seat to Defend Truvada*[®], FIERCE PHARMA (May 17, 2019), <https://www.fiercepharma.com/pharma/gilead-s-o-day-takes-congressional-hot-seat-to-defend-Truvada>.

224. *United States v. Gilead Scis., Inc.*, 2019 WL 5942984 (D. Del.) (Trial Pleading).

225. *The United States of America v. Gilead Sciences, Inc.* 1:19CV02103 (referring to a sealed Motion for Summary Judgment at Docket Entry 360).

from Gilead's sharing of their Truvada.²²⁶ The judge ruled that the CDC did breach the MTA.²²⁷ In May 2023, a jury found for Gilead in the patent suit, finding both the CDC's patents invalid and not infringed by Gilead's sale of Truvada for PrEP.²²⁸

IV. ANALYSIS OF INNOVATION DRIVERS

The motivations and impediments to the actors in the three-decade-long story of Truvada innovation changed throughout the HIV/AIDS pandemic. At the pandemic's start in the United States in the early 1980s, vulnerable communities and federal health authorities were forced to reckon with the most lethal yet transmissible virus in recorded human history, yet they knew nothing about the disease itself. AIDS activists, quietly ostracized and blamed by conservative society for their plight, cried out and protested for help. Interest in the international scientific community to address the massive AIDS crisis by engaging with patients and health authorities birthed an organized AIDS innovation ecosystem.

In the late 1980s and early 1990s, the ongoing crisis and the new ecosystem of AIDS activists and researchers helped motivate university chemists to synthesize what would become the two compounds in the Truvada combination therapy. The university scientists had motivations and challenges unique to their projects and personalities, but they each sought patent protection of their novel ARTs and leveraged the patents to commercialize their technologies via licenses to pharmaceutical companies for clinical development. Pharmaceutical companies managed dueling interests of responding to the public health crisis and fulfilling their fiduciary duties to corporate shareholders in gradually developing the components of Truvada.

After Truvada was marketed, AIDS activists and health authorities maintained the innovation ecosystem for decades to: further efforts to continue reducing case numbers; continue increasing the longevity of HIV patients; and spur trials for PrEP to prevent HIV infection. HIV became manageable, but many of the same motivations driving innovation in mid-1981 remain today: to stop HIV from spreading and to help those with less resources combat the virus.

226. See *Gilead Scis., Inc. v. United States*, 151 Fed. Cl. 742 (2020).

227. Andrew Karpan, *Claims Court Finds CDC Broke Gilead Deal Over HIV Research*, LAW360 (Nov. 22, 2022), <https://www.law360.com/articles/1551976/claims-court-finds-cdc-broke-gilead-deal-over-hiv-research>.

228. See The Editorial Board, *Gilead Sciences Defeats the CDC*, WALL ST. J. (May 10, 2023) (sharing the jury verdict of noninfringement and CDC patent invalidity), <https://www.wsj.com/articles/cdc-federal-jury-gilead-sciences-truvada-patent-4ae9fa8e>.

A. THE 1980S: INNOVATION IN RESPONSE TO ACUTE CRISIS

The chaos of the first decade of the U.S. HIV/AIDS epidemic created many innovation drivers behind the development of Truvada. The then-unprecedented nature of the pandemic motivated regular citizens to call on the government to act. The government, though slowed by stigma and misunderstanding, eventually responded. Private actors—scientists and pharmaceutical companies—turned their research quickly to finding solutions for the ballooning problem of HIV/AIDS. As the scale of the humanitarian crisis unfolded in this first decade, international bodies and nonprofits increasingly formed and became leaders in this innovation ecosystem. These actors together started a unique ecosystem of innovation to end the HIV/AIDS pandemic.

1. *Activism Borne from Communities' Unanswered Cries for Help*

As of early 2023, HIV/AIDS is the deadliest pandemic in human history (COVID-19 has killed only about 20% as many people globally as AIDS has as of early 2023²²⁹), largely because of the rapid spread of HIV/AIDS in the decade immediately following the U.S. onset of the pandemic in 1981.²³⁰ The sheer number of dead in vulnerable communities—men who have sex with men (“MSM”), people with close contact to people in sub-Saharan Africa, hemophiliacs, and intravenous drug users—has *devastated* these communities.²³¹ However, most of these communities in Western society were already disadvantaged: gay men, Black Americans, and people with disabilities, though gay men quickly became the largest patient population in the United States.²³² A temporary official name for the virus (“Gay-Related Immune Disorder”) only added to existing homophobia and transphobia.²³³

The situation was even more dire in sub-Saharan Africa, where most deaths due to HIV/AIDS have occurred since the pandemic began.²³⁴ While HIV spread mostly in a select few marginalized communities in the United

229. See Steven W. Thrasher, *Why COVID Deaths Have Surpassed AIDS Deaths in the U.S.*, SCI. AMERICAN (Dec. 1, 2021), <https://www.scientificamerican.com/article/why-covid-deaths-have-surpassed-aids-deaths-in-the-u-s/#:~:text=While%20COVID%20deaths%20are%20now,who%20have%20died%20of%20AIDS.>

230. See *supra* Section II.A.

231. See *supra* Section III.A.1; see also Shilts, *supra* note 10, at 42, 72.

232. See *supra* Section III.A.1.

233. One of the CDC's first names for the AIDS condition was Gay-Related Immune Disorder, or GRID, only adding to the blaming and shaming of the MSM community. See, e.g., Lawrence K. Altman, *New Homosexual Disorder Worries Health Officials*, N.Y. TIMES (May 11, 1982), <https://www.nytimes.com/1982/05/11/science/new-homosexual-disorder-worries-health-officials.html> (discussing GRID in a way that added to stigma of the MSM community).

234. See Thrasher, *supra* note 229.

States and other Western countries, in sub-Saharan Africa it spread among the broader population, including through childbirth.²³⁵ These communities faced hunger, lacked access to Western medicine (including early HIV treatments), and confronted many other challenges largely avoided by Western society making HIV/AIDS containment especially difficult.²³⁶

Facing serious impediments by their own governments, people in affected communities across the world had no choice in this period but to advocate for their own survival.²³⁷

2. *The U.S. Federal Government and International Diplomacy Slowly Step Up*

The association of AIDS with disadvantaged groups, especially MSM, was a major impediment to the U.S. government's public health response. In 1981, the federal government was riding a new socially conservative wave following the decades focused on social tolerance in the 1960s and 1970s.²³⁸ Social conservatives were in charge of the Presidency and the Senate for much of the crisis' first decade in the United States.²³⁹ Federal action therefore required conservative, often religious, constituencies to recognize the plight of Americans conservatives often looked down on, blamed for the burgeoning crisis, or both.²⁴⁰ President Reagan only publicly acknowledged the crisis for the first time in 1985 and only first signed legislation and an executive order creating public health research initiatives to fight AIDS in 1987, six years after the pandemic began in the United States.²⁴¹ In that time, nearly fifty thousand Americans had already died from AIDS-related complications.²⁴² Prejudices seemed to impede the U.S. government from caring for its own people.

The silence of the U.S. federal government in those early days turned patients, doctors, families, and friends of HIV/AIDS patients into activists.

235. *See id.*

236. *See id.*

237. *See supra* Section III.A.3.c.

238. *See generally* *The People vs. America*, AL JAZEERA, <https://interactive.aljazeera.com/ajc/2017/the-people-vs-america.html> (last visited May 21, 2023) (providing a chronology of sociopolitical development in the 20th century United States by decade).

239. *See* *The People vs. America: 1980s – A new era of conservatism*, AL JAZEERA, <https://interactive.aljazeera.com/ajc/2017/the-people-vs-america/1980s.html> (last visited May 21, 2023).

240. *See* President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54; *see also supra* Section III.A.3.c.

241. *See supra* Section III.A.1.

242. Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report: HIV and AIDS — United States, 1981-2000*, CDC.GOV (June 1, 2001), <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5021a2.htm>.

These communities needed care that generally did not yet exist or, if it did, patients were not receiving it.²⁴³ AIDS activism, especially the in-person protests at each of the major health authorities—NIH, National Institute of Allergy and Infectious Diseases (NIAID), FDA, CDC—is credited by leaders in those agencies as creating federal support for research and development of HIV medicines.²⁴⁴ The FDA created its first accelerated drug approval processes in response to AIDS pandemic, but, more directly, in response to the ACT UP protestors shutting down their building.²⁴⁵ The AIDS activists' work on this front paid off in the 1990s and later in the accelerated approval of Truvada and its component drugs, Viread and Emtriva, for HIV treatment.²⁴⁶ Many activists passed away in the 1980s and 1990s fighting for the care they would not receive.

3. *Growing Crisis Motivated a Unique Public-Private Innovation Ecosystem*

The AIDS innovation coalition built itself slowly in this period in response to the patients' and physicians' cries for help. With “highly toxic” AZT being the first treatment brought (six years into the pandemic), the existing HIV therapy options were wildly inadequate well into the mid-1990s.²⁴⁷ However, pharmaceutical companies increasingly sought to capture the HIV therapy market²⁴⁸ and annual International AIDS Conferences shared discoveries among innovators in public health and private companies.²⁴⁹

AIDS increased dramatically in sub-Saharan Africa concurrent with and persisting beyond the pandemic in developing nations.²⁵⁰ The expanding humanitarian crisis prompted massive philanthropy and international policymaking to increase access to AIDS treatments globally.²⁵¹ Philanthropic and non-governmental organizations were truly driven by the scope of suffering due to AIDS in developing parts of the world.²⁵² These nations

243. *See supra* Section III.A.1; *see also supra* Section III.A.2.b.

244. *See supra* Section III.A.3.a.

245. *See id.*; *see also supra* Section III.A.3.a.

246. *See supra* Section III.A.3.c; *see also supra* Section III.C.1.b.

247. *See supra* Table 1 (showing HIV drug approval dates as mostly in 1990s and later); *see also supra* Table 2 (showing toxicity concerns with many of the early drugs listed in Table 1).

248. *See, e.g.*, THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (sharing Gilead's motivations for getting into the HIV treatment marketplace primarily at the 20 minute mark, and its expansion of HIV treatment voluntary licensing globally at the 38 minute mark).

249. *See* Khai Tram, *A Brief History of the International AIDS Conference*, GATESNOTES (July 18, 2012), <https://www.gatesnotes.com/A-Brief-History-of-the-International-AIDS-Conference#:~:text=Atlanta%20%201985%3A%20The%20first%20IAC,on%20the%20emerging%20new%20disease.>

250. *See supra* Section IV.A.1.

251. *See supra* Section III.A.3.b.

252. *See id.*

became the primary sites for federal health authorities and pharmaceutical companies to prove the effectiveness of HIV therapies in humans via clinical trials.²⁵³

Therefore, the African and other developing nations most severely afflicted by the HIV/AIDS pandemic were highly motivated when they began a diplomatic effort in this period to drastically improve access to the novel and limited Western medicines against HIV. This diplomacy would culminate in the 2001 Doha Declaration regarding the international TRIPS Agreement allowing nations to issue compulsory licenses to patented technologies critical to the health and welfare of a nation's people.²⁵⁴ This agreement had a tremendous impact on how pharmaceutical companies, such as Gilead, would choose to enter voluntary license agreements with developing countries for valuable HIV treatments. Voluntary licensing programs encouraged peaceful, increased distribution of the lifesaving drugs while avoiding the consequences of a nation issuing a compulsory license for a company's technology. Without the Doha Declaration on TRIPS, it is not clear that pharmaceutical companies like Gilead would have had as much motivation to offer these voluntary licenses in the first place.²⁵⁵

Drivers in the marketplace—patient adherence, desirable lifelong treatments, minimizing drug toxicities, profitability of treatments, and altruism—began to become clear in this dire period. First, prior to Truvada, HIV/AIDS patients took several, even a dozen or more medications daily for HIV treatment, often multiple times per day, making treatment adherence challenging.²⁵⁶ Second, HIV, by its nature, was (and still is) difficult, if not impossible, to cure.²⁵⁷ A lifelong prescription presents a large business opportunity. Third, combination use of therapies was often prescribed off-label, with the potential for high toxicity for those in advanced stages of the disease.²⁵⁸ Many initial HIV treatments bore long-term adverse effects or

253. See, e.g., *supra* Section III.C.2.a.

254. See *supra* Section III.A.3.b.

255. See *id.*

256. See, e.g., THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (describing near the 16 minute mark the strict dosing schedule faced by most AIDS activists that met with Gilead in the 1990s); see also '397 Patent, *supra* note 2, at col. 19:27-30 ("Combinations of the present invention [Truvada] enable patients greater freedom from multiple dosage medication regimens and ease the needed diligence required in remembering and complying with complex daily dosing times and schedules.").

257. See *supra* Section II.A.

258. See *supra* Table 2 (showing the many toxicities for many individual HIV treatments and does not list all the adverse interactions among their combinations).

toxicities that harmed patients' health and discouraged treatment adherence.²⁵⁹ Other HIV treatments contributed to "viral resistance," where a fought-down HIV viral load would rebound and become resistant to the prior treatment because of a lack of effective combination therapy that the virus couldn't dodge evolutionarily.²⁶⁰ Pharmaceutical inventors and companies saw a huge business opportunity: a once-a-day, one-a-day combination therapy pill to treat HIV could dominate the market.²⁶¹ Desperate customers and a genuine public health crisis made for strong motivators for scientists and pharmaceutical companies to research novel treatments in this area.

Yet there were still impediments to HIV treatment development that the ecosystem collaborated to remove in this period. First, the ecosystem was new and required time and talent to form. Unfortunately, established pharmaceutical companies found these new HIV departments higher-risk ventures and de-prioritized them in high-profile mergers and acquisitions, such as those mergers between Glaxo and Burroughs-Wellcome and between Bristol-Myers and Squibb.²⁶² Second, the regulatory burdens in place by the FDA and USPTO for HIV/AIDS inventions were just as high in the first years of the pandemic as for all other drugs. The FDA passed "Subpart H" for accelerated approval of life-saving drugs (such as HIV therapies) in direct response to the AIDS activism at their doorstep in the late 1980s and early 1990s.²⁶³ This FDA regulatory change enabled the innovation ecosystem to launch many life-saving ARTs in the mid-1990s.²⁶⁴

B. THE INNOVATORS BEHIND TRUVADA FOR HIV TREATMENT

The innovators behind each part of the breakthrough HIV treatment drug Truvada at times revealed how their innovations were driven: (1) in university laboratories, by strokes of genius, brute force, concern for the crisis, and entrepreneurial spirit; and (2) in commercialization, by risk-taking startups

259. *See id.* (providing HIV treatment toxicity / adverse effect information by drug class and drug name).

260. *See id.*

261. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (sharing Gilead's motivations for getting into the HIV treatment marketplace at the 20 minute mark).

262. *See supra* Section III.B.1.b; *see also supra* Section III.B.2.b.

263. *See Understanding the History and Use of the Accelerated Approval Pathway, supra* note 96; *see also Accelerated and Restricted Approvals Under Subpart H (drugs) and Subpart E (biologics)*, FDA.GOV (Aug. 6, 2014), <https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/accelerated-and-restricted-approvals-under-subpart-h-drugs-and-subpart-e-biologics>.

264. *See Accelerated and Restricted Approvals Under Subpart H (drugs) and Subpart E (biologics)*, FDA.GOV (Aug. 6, 2014), <https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/accelerated-and-restricted-approvals-under-subpart-h-drugs-and-subpart-e-biologics>.

believing in the size of the market, expressing altruistic concern for the situation, engaging in regulatory accelerated approval pathways, and seeking regulatory exclusivity. Moreover, patents were used by every inventor and pharmaceutical development leader at every stage of the Truvada development process. A recurring theme emerges from the tenofovir, emtricitabine, and combination therapy stories: patent licensing was key to the series of pharmaceutical mergers and acquisitions that enabled company growth—and more importantly, high-quality HIV treatment development.

1. *Creators of Tenofovir*

Innovation drivers, such as genius and brute force, underpinned the academic chemists' synthesis of tenofovir; impediments, such as inconsistent collaboration with a large pharmaceutical company, Bristol-Myers, slowed their progress. These are often distinct from the drivers (like agility and brute force), or the impediments (like limited financing) faced by their biopharmaceutical company development partner, Gilead Sciences, Inc.²⁶⁵

a) Holý of the Czech Academy of Sciences

Holý's work on tenofovir was driven by many forces of innovation: genius, brute force, patent ambitions, curiosity, and more. He also faced challenges pursuing the invention.

i) Holý's Drivers

Holý created an antiviral molecule by modifying a nucleoside analogue, DHPA, and sought to apply it to many viral diseases (herpes simplex virus, hepatitis B virus, and HIV).²⁶⁶ In this way, Holý had a stroke of genius for realizing transcription enzymes of many different viruses could be inhibited by the same DHPA-based compounds.

Holý's efforts also required brute force. He tried small tweaks to DHPA against a wide swath of viruses, choosing not to limit his research to only his initial target virus, herpes simplex (though DHPA derivatives were successful against HSV as well).²⁶⁷ Tenofovir, one of Holý's DHPA derivatives, ended up proving a more targeted antiviral than DHPA.²⁶⁸ In the end, his modifications

265. See generally *supra* Section III.B.1.

266. See *id.*; see also Hocek, *supra* note 103.

267. See Hocek, *supra* note 103 (summarizing Holý's major inventions and other accomplishments over his career); see also De Clercq et al., *supra* note 106, at 563–65.

268. See Erik De Clercq & Guangdi Li, *Approved Antiviral Drugs over the Past 50 Years*, 29 CLINICAL MICROBIOLOGY REVS. 695, 721 (2016).

of the DHPA molecule led to treatments for HIV (including the tenofovir component of Truvada), cytomegalovirus, hepatitis B, and herpes.²⁶⁹

Holý was also motivated to build a patent portfolio for his work as a chemist. He was quick to file patents on the DHPA and tenofovir technologies.²⁷⁰ Over the course of his decades-long career, Holý filed over 60 patent applications, many of them granted.²⁷¹ This patent portfolio could indicate personal fortune through licensing his patents, institutional reputation, professional promotion, or all the above motivated him. The Czech Academy of Sciences, where he developed the chemistry supporting the first patents to tenofovir, was assigned all the rights to these patents.²⁷² In this manner, the Academy managed patent rights in a similar capacity to universities in the United States under the Bayh-Dole Act, where American universities are assigned the patent rights of employed innovators to encourage universities to commercialize their innovations.²⁷³

Holý may have been motivated by further professional recognition or career advancement, but there is limited evidence to available to the public on these points—after all, he was already the chair of his department when he filed the first U.S. patent.²⁷⁴ Though there is limited evidence in public that he was specifically motivated by an altruistic desire to help end the HIV crisis, his curiosity and desire to cure herpes simplex virus combined with thorough testing of other virus' reactions to DHPA derivatives imply he was also motivated to address as many public health virological issues as he could.²⁷⁵

Due to Holý's position as chair of the biochemistry department at the Czech Academy of Sciences while developing DHPA, he had few impediments to accessing necessary research tools.²⁷⁶ Given his leadership position at the time, it is less clear that Holý would develop this thread of antiviral technologies for mostly financial reward instead of genuinely trying to address public health.

269. *See id.*; *see also* Hocek, *supra* note 103 (summarizing Holý's major inventions and other accomplishments over his career).

270. *See, e.g.*, '716 Patent, *supra* note 270.

271. *See, e.g., id.*; *see also* Hocek, *supra* note 103.

272. *See, e.g.*, '716 Patent, *supra* note 270.

273. *See generally* Bayh-Dole Act, *supra* note 97.

274. *See* Hocek, *supra* note 103.

275. *See supra* Section III.B.1.a.

276. *See* Hocek, *supra* note 103.

ii) Impediments to Holý's Tenofovir Research

Holý faced a challenge when Bristol-Myers stopped preclinical development of tenofovir as an antiviral for HIV in 1989.²⁷⁷ However, this impediment was brief. Gilead restarted this work within the next two years.²⁷⁸

b) Drivers for Bristol-Myers and Gilead

Bristol-Myers and Gilead, the two companies that worked in series on the preclinical and clinical development of tenofovir for HIV treatment, had some similar and some distinct motivations and impediments in their work on tenofovir.²⁷⁹ Bristol-Myers was an established large pharmaceutical company; Gilead was only a small biopharmaceutical startup at the time. Both were motivated to find a tenofovir prodrug that would allow for an oral drug formulation. Some scientists moved from larger companies to a smaller company to develop HIV drug candidates with less strategic resistance to their vision of the value of new HIV treatments. Gilead, as a small and new company, could nimbly explore many prodrugs, within somewhat more constrained resources.

i) Motivations and Impediments for Bristol-Myers

Bristol-Myers initiated tenofovir development through licensing patents from the Czech Academy of Sciences in the late 1980s. It sought to develop an HIV ART that was safer and more effective than AZT and others coming to the market. Yet in the 1989 merger with Squibb, Bristol-Myers decided to gut the HIV therapy development department.²⁸⁰ Reasons for this decision were not publicized but may have included to pursue lower-risk product portfolios due to the then-nascent field of HIV science. The director of that department, Martin, wanted to continue the development of HIV therapies. Martin had become a part of the AIDS innovation ecosystem and felt a connection to the public health crisis. To the impediment of Bristol-Myers' individual development of other life-saving drugs, Martin found an opportunity to continue this life-saving work at then-startup Gilead.²⁸¹

ii) Motivations for Gilead

Gilead, as a startup, was motivated to find the breakthrough technologies that would put them on the map with investors and then turn a profit by

277. *See id.*

278. *See supra* Section III.B.1.b.

279. *See generally supra* Section III.B.1.

280. *See id.*

281. *See id.*

developing them clinically. Their motivations reflect the aggressive actions they took to execute these strategies.

The first innovation driver for Gilead was their ability to hire leading HIV researchers due to Bristol-Myers' cuts, including Martin.²⁸² With the flexibility and agility of a fledgling Silicon Valley startup, Gilead's founding CEO Riordan hired Martin and listened to his advice on where to take the startup from a technology standpoint. Together they took Gilead in the direction of NRTI/NtRTI development and away from the "antisense" technology upon which Riordan had founded Gilead.²⁸³

A second innovation driver for Gilead was the availability of licenses due to Bristol-Myers' cuts. Because Bristol-Myers shelved most HIV projects after the merger with Squibb, including development of tenofovir, a clause in the license agreement with Czech Academy of Sciences allowed the Academy to generate a new exclusive tenofovir patent license, which gave Martin and Gilead an opening to license tenofovir technology.²⁸⁴

Gilead's most critical innovation driver was its brute force development of many prodrugs of tenofovir. TDF and other Gilead prodrugs such as tenofovir alafenamide fumarate (TAF) are both now staple products in HIV and even hepatitis B virus treatment.²⁸⁵

Gilead patented many prodrug combinations for tenofovir, including TDF. Gilead successfully commercialized TDF alone as Viread.²⁸⁶

iii) Impediments for Gilead

Gilead faced headwinds as a startup, from its initial technology platform selection to the financing challenges often faced by startups.

The "anti-sense" technology that Riordan envisioned for the fledgling company was challenging to develop. Fortunately, Riordan course-corrected by hiring Martin and listening to his ideas about how Gilead could become the world's best antiviral company.²⁸⁷

Limited funding and people constrained Gilead during the bulk of the tenofovir preclinical development. However, Gilead attracted sufficient investors by doing its work finding safe ARTs.²⁸⁸

282. *See id.*

283. *See id.*

284. *See supra* Section III.B.1.b.

285. *See id.*

286. *See id.*

287. *See id.*

288. *See id.*

2. *Creators of Emtricitabine*

The chemists at Emory University had distinct motivations and faced distinct impediments in their work synthesizing the emtricitabine NRTI product from the motivations and impediments faced by their series of pharmaceutical company development partners, Burroughs-Wellcome, Triangle, and Gilead.

a) Liotta's Motivations and Impediments in the Synthesis of Emtricitabine

Liotta's work on tenofovir was driven by many forces of innovation: entrepreneurial spirit, genius, incremental advances on existing research, brute force, curiosity, serendipity, wide patent ambitions, and more. Yet, Liotta too faced challenges pursuing the invention to commercialization, especially in the form of patent litigation.

i) Liotta's Motivations

Liotta has considered himself a “serial entrepreneur”—consistently creating molecules to try to be the next big drug, not just for fundamental research, and building ties to venture capital and large pharmaceutical companies as potential licensing partners.²⁸⁹ In this way, Liotta appears to have been motivated to some extent either by the rush of starting new businesses from scratch, the potential profits from such activities, the reputational benefit to his laboratory for doing so, or a combination of the three.²⁹⁰ This entrepreneurial skill helped Liotta launch emtricitabine before his competitors because he could leverage a “long-standing collaboration” with Burroughs-Wellcome scientist Painter to help initiate preclinical trials and other development steps.²⁹¹

Liotta partnered with Schinazi, a virologist also at Emory University. Schinazi observed a cytosine analogue molecule presented as a racemic mixture of two enantiomers at the 1989 International AIDS Conference and suggested Liotta create a more efficient synthesis that purified it further into each enantiomer to develop a powerful anti-HIV ART.²⁹² Through their novel synthesis and isolation process to obtain only one enantiomer, 3TC, where the

289. See Dr. Dennis Liotta, *supra* note 137.

290. See *id.*

291. See Liotta & Painter, *supra* note 138, at 2093.

292. See *id.* at 2092.

presenter had not, Liotta and Schinazi acted under both the innovation drivers of genius and of building on others' discoveries.²⁹³

Liotta applied brute-force methods of attempting many different synthesis paths for the cytosine analogues. He applied his organic chemistry expertise to develop a more-efficient emtricitabine synthesis than his Yale, the University of Georgia, and Glaxo competitors in the race to innovate the best cytosine/cytidine analogs as antiviral drug candidates.²⁹⁴ This way, he found that fluorinating (adding fluorine) a starting enantiomer mixture created a racemic mixture that was just as effective, or more effective, than the (-) enantiomer of the non-fluorinated cytosine analog.²⁹⁵ Liotta had been attempting "a variety . . . of nucleoside analogs and evaluating their anti-HIV profiles" but it was pure serendipity that one of those attempts—the fluorinated version—was also *better* metabolized by a patient's cells than the reference cytosine analogue.²⁹⁶ Liotta had serendipitously created the breakthrough HIV drug FTC, or emtricitabine.

Liotta was also an avid believer in the patent system. As of 2023, he holds more than 100 patents²⁹⁷ and has fought many patent litigations directly, to both his and Emory University's financial benefit. Emory University owned the first patents to emtricitabine and its precursors and won a patent litigation against the Canadian scientist who presented the precursor molecule at the 1989 International AIDS Conference inspiring Liotta's work.²⁹⁸ Liotta, who remains at Emory, would help Emory negotiate a sale of the patent rights on emtricitabine to Gilead Sciences.²⁹⁹

Liotta was less clearly motivated by the search for tenure at the time of the invention, because he was Chair of Emory's Chemistry Department from 1993–96.³⁰⁰ He appears to be partially driven by recognition and esteem in his field, having won the Perkin Medal in 2022.³⁰¹ Liotta's prior statements suggest he had curiosity in creating emtricitabine and other antivirals driven partly by

293. See *Emory Univ. v. Glaxo Wellcome Inc.*, No. 1:96-CV-1868-GET, 1997 WL 817342 (N.D. Ga. July 14, 1997), at *4, *9 (describing how Emory's patent claimed isolation of FTC where Glaxo's patent only claimed the racemic mixture, not FTC in isolation, and denying Glaxo summary judgment partially on this basis).

294. See *supra* Section III.B.2.a.

295. See Liotta & Painter, *supra* note 138, at 2094.

296. See *id.*

297. See Dr. Dennis Liotta, *supra* note 137.

298. See *supra* Section III.B.2.a.

299. See *id.*

300. See Dr. Dennis Liotta, *supra* note 137.

301. See *id.*

a desire to address the terrible AIDS public health crisis and other “viral diseases of global concern.”³⁰²

ii) Impediments Faced by Liotta in Synthesis of Emtricitabine

Liotta’s primary impediments to his development and commercialization of emtricitabine came in the form of several patent litigations arising from the early stages of emtricitabine development: both (1) the infringement as well as the ownership and inventorship disputes related to the 1989 International AIDS Conference; and (2) from his work to license emtricitabine to Barry’s startup Triangle Pharmaceuticals after Burroughs-Wellcome stopped pursuing emtricitabine’s development during the merger with Glaxo.³⁰³ Though the litigations drained Liotta’s time and slowed Triangle’s progress on emtricitabine, he did ultimately prevail in each suit.³⁰⁴

b) Drivers and Impediments for Burroughs-Wellcome and Triangle

The innovation drivers in the commercialization of emtricitabine share many similarities with those in the commercialization of tenofovir. Large pharmaceutical company Burroughs-Wellcome sought to merge with a competitor, Glaxo, and, to minimize risk, cut Glaxo’s HIV therapy development projects, including emtricitabine. The spearhead for that division at Burroughs-Wellcome, Barry, would go on to form his own small pharmaceutical company, Triangle, to continue emtricitabine development.

i) Motivations and Impediments for Burroughs-Wellcome

Burroughs-Wellcome shared the same drivers to commercialize emtricitabine that its peer company Bristol-Myers had to commercialize tenofovir: access to a promising technology via licensing; an altruistic desire to develop a clinically safe and effective breakthrough HIV treatment; a large and profitable market opportunity; and bring profit to its shareholders through a merger with a competitor, though this last motivation was equally an impediment to emtricitabine’s short-term development.³⁰⁵

Also, like Bristol-Myers, Burroughs-Wellcome faced a contractual impediment: if it stopped pursuing clinical development from its licensed patent with Liotta, Liotta and Emory had the right to re-license the patent exclusively to another entity to restart the drug development.³⁰⁶ However, this

302. *See id.*

303. *See* Liotta & Painter, *supra* note 138, at 2096.

304. *See id.*

305. *See supra* Section IV.B.1.b.

306. *See supra* Section III.B.2.a.

license agreement clause enabled Liotta and Emory University to take emtricitabine's development elsewhere: to Triangle Pharmaceuticals, Inc.

ii) Motivations for Triangle

Barry, an HIV scientist at Burroughs-Wellcome and part of the original team of AZT creators, wanted to continue pursuing emtricitabine's clinical development when Burroughs-Wellcome terminated the project after the merger with Glaxo.³⁰⁷ When Burroughs-Wellcome abandoned development of emtricitabine, Barry left—just as Martin departed from Bristol-Myers.³⁰⁸ He exhibited entrepreneurial spirit and founded his own small pharmaceutical company: Triangle. Burroughs-Wellcome, like Bristol-Myers, triggered a release clause in their patent license agreement (for emtricitabine, licensed from Emory), allowing re-license of the molecule from Emory, in this case, to Triangle.³⁰⁹

Barry may have been specially motivated to continue HIV therapy development to improve upon his initial helpful (yet toxic) AZT drug at Burroughs-Wellcome.³¹⁰

iii) Impediments Faced by Triangle

Triangle, as a startup, faced challenges that Gilead had encountered only a few years earlier—limited funding and manufacturing capacity to make rapid progress.³¹¹ Yet, Triangle faced distinct challenges in the patent litigations brought against it, Liotta, and Emory University, by Glaxo and the scientist who inspired Liotta's work.³¹² Further, Barry died tragically early, leaving the fledgling company without its specially motivated leader. It was beneficial for the company, then, that Gilead found Triangle and its emtricitabine technology to be promising and worthy of acquisition.³¹³

C. TRUVADA COMMERCIALIZATION: GILEAD AND PUBLIC SECTOR INNOVATION

Gilead took center stage for HIV treatments in 2001–02, when it received FDA approval for its potent TDF drug (Viread) and negotiated the acquisition of Triangle to fully commercialize emtricitabine and combine it with TDF as Truvada. As public health organizations and agencies driven to mitigate the

307. *See supra* Section III.B.2.b.

308. *See supra* Section IV.B.1.b.

309. *See supra* Section III.B.2.b.

310. *See id.*

311. *Compare id. with* Section IV.B.2.

312. *See supra* Section IV.B.2.a.

313. *See supra* Section III.B.2.b; *see also supra* Section III.C.1.a.

HIV pandemic in new ways took notice of Gilead's HIV treatments, the organizations incorporated Gilead's treatments into trials for public health's next big goal in HIV treatments for that decade: to find a preventive technology. The AIDS innovation ecosystem finally succeeded in doing so with Truvada for PrEP.

1. *Truvada as HIV Treatment: Gilead the David Turned Gilead the Goliath*

Many innovation drivers motivated and assisted Gilead to launch its blockbuster combination ART against HIV (Truvada). They include: an interest in carrying out a specific brand vision for the company; curiosity; leaders' expertise in HIV therapeutic development; resources to build targeted intellectual property portfolios; institutional collaboration across the AIDS innovation ecosystem; unmet patient need for a once-a-day single pill form of HIV treatment; and resources to acquiring companies and technologies to achieve these broader goals. Gilead's main challenges in this process have arisen out of the Doha Declaration and patent litigation on the Truvada active ingredients or methods of use.

a) Gilead's Motivations for Truvada

Gilead was founded by Riordan and expanded dramatically under Martin, who both sought to build the world's leading antiviral company. Riordan sought to leverage his degrees in engineering, medicine, and business as Gilead's founder.³¹⁴ The leaders' goal for Gilead to be the best antiviral maker was consistent with Riordan's initial vision of Gilead as finding treatments for viruses like the flu, common cold, and other common viruses that get in everyday people's way.³¹⁵ However, Martin had high ambitions for Gilead to be the leader in ART treatments against HIV, restarting his work from his time at Bristol-Myers on tenofovir to take Gilead down that path.³¹⁶ One of Martin's first actions as the second CEO of Gilead (after Riordan retired) was Gilead's acquisition of Triangle to develop market-leading combination therapy for HIV (as Truvada and later Atripla).³¹⁷

The local community in which Gilead has based its operation likely was a driver of its innovation in the HIV space. Gilead's headquarters in San Francisco enabled it to connect with the large Bay Area queer community and HIV patient population, to learn their needs, and to learn how Gilead medicines including ARTs that patients will want to take, could improve their

314. *See supra* Section III.B.1.b.

315. *See id.*

316. *See id.*

317. *See supra* Section III.C.1.a.

quality of life.³¹⁸ Gilead developed relationships with AIDS activists during Viread development and leveraged them in the decades that followed to help growth of their HIV product line (including Truvada, Truvada for PrEP, and more).³¹⁹ These relationships motivated Gilead to develop a once-a-day, one-pill treatment. Gilead leadership was aware of the loud and sad four-eight-twelve dose alarms that most HIV patients interacting with them used to consistently take their cocktails of multiple HIV treatments.³²⁰ From this angle, Gilead could also see the profit potential from the higher concentration of suffering in the HIV patient community locally than elsewhere.

Gilead was motivated by and secured regulatory exclusivities on its HIV products as they came to market. Gilead received New Chemical Entity status on tenofovir (“Viread”) and fast-tracked FDA approval in 2001; they also received both for emtricitabine (“Emtriva”), approved in 2003.³²¹ Gilead was able to secure accelerated approvals of Truvada through simple bioequivalence studies with its established tenofovir and emtricitabine products, allowing rapid Truvada FDA approval in 2004.³²²

The highly accelerated approvals also reflected public health institutions’ support of Gilead in helping each product hit the market. This institutional support for Gilead’s work was also shown by the agencies’ collaboration with Gilead on PrEP development—including agencies such as NIH/NIAID, the Bill and Melinda Gates Foundation, and other nonprofits.³²³ Gilead signed material transfer agreements (MTAs) with public health authorities to provide Truvada-related supplies for clinical trials for PrEP globally in 2001–11.³²⁴ Through this process, the public health authorities began pushing for PrEP and patenting it on their own. The CDC either intentionally or inadvertently patented Truvada for PrEP and recently lost a patent infringement litigation against Gilead.³²⁵

It appears that for brand or market power or both, Gilead chose a strategy of horizontal integration, opting to buy or license from companies making

318. See, e.g., THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (containing clip of Norbert Bischofberger, EVP of R&D at Gilead Sciences, sharing motivations and goals for Atripla and Truvada for HIV treatment at the 20-minute mark).

319. See *supra* Section III.B.1.b.

320. See THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (describing the 4-8-12 dosing regimen of the first anti-HIV treatments near the 16 minute mark).

321. See *Drug Approval Package: Emtriva® (emtricitabine) 200 mg Tablets*, *supra* note 179; see also *Drug Approval Package: VIREAD® (Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 130.

322. See *Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 30.

323. See *supra* Section III.C.2.a.

324. See *id.*

325. See *id.*

ideal active ingredients to use in combination anti-HIV therapies. Buying Triangle for emtricitabine for roughly \$400 million and paying outright for the patent rights (around \$500 million to Emory) supports this theory.³²⁶ It is notable that Gilead took this unusually aggressive step instead of partnering with Triangle to make combination drugs with emtricitabine, which may have been cheaper to manage for a year or two, but not for the life of the patented invention.³²⁷

Gilead also made a point to gather patents and other intellectual property (IP) from other sources to help build a targeted portfolio. Gilead turned to Emory and Triangle for acquiring emtricitabine, but also licensed from Czechoslovak Academy of Sciences in Prague under a long-term agreement to develop and commercialize tenofovir.³²⁸ Gilead's extensive testing of different prodrugs of tenofovir for effective metabolism could also be used to support this theory, as they now have a wide array of prodrugs (and corresponding IP protection) to use to expand their product line.³²⁹

b) Impediments to Gilead's Commercialization of Truvada

Gilead chose to address a public health crisis with its development of HIV treatment, so it has had to respond to international law and policy related to the AIDS crisis. The most major development on this front, TRIPS—the international compulsory licensing system under the World Trade Organization and its 2001 Doha Declaration—pushed Gilead to create a global voluntary licensing program. This program includes licensing their ARTs to third-party local manufacturers in developing nations to produce the same medications at lower cost. In this program, Gilead has negotiated lower rates on its HIV ARTs with developing countries so that it could minimize the number of compulsory license demands by governments, who have only acted on their compulsory license rights a few times for the Truvada active ingredients.³³⁰

Gilead has had to fend off patent litigation from the CDC and others over the Truvada technology, including design defect suits due to the availability of other prodrugs. However, Gilead has largely succeeded in these cases and managed to avoid major compulsory license fights, so these impediments have not severely hindered its growth.³³¹

326. *See supra* Section III.C.1.a.

327. *See id.*

328. *See supra* Section III.B.

329. *See supra* Section III.B.1.b.

330. *See id.*

331. *See supra* Section III.C.2.c; *see also infra* Epilogue (describing the Truvada design defect tort case).

2. *Truvada for PrEP: Public Health Goals Mix with Wide Profitability Potential*

International philanthropic organizations like the Bill and Melinda Gates Foundation were eager to provide support for new technologies that could contain the HIV/AIDS pandemic. Public health institutions were coalescing at the time of the FDA's approval of Viread in 2001 around the idea that HIV ARTs should be attempted as post-exposure prophylaxis (preventive drugs after exposure). Investments in the then-proposed target population coincidentally benefitted PrEP treatment research, which Gilead eventually pursued despite being advised against doing so by certain AIDS activists concerned with changes in the MSM community if PrEP became prevalent.

a) Public Health Goals

The AIDS innovation ecosystem had many motivations to find and launch a PrEP product against HIV. First, the actors involved all wanted to protect vulnerable communities from HIV transmission. The ecosystem wanted to stem the persistent tide of new infections each year, even decades later. This has been especially true for the vulnerable populations in sub-Saharan Africa that have been massively afflicted by the HIV/AIDS pandemic and where most AIDS deaths have been since the 1990s.³³²

However, experts questioned whether this strategy would actually bring case rates down in the United States.³³³ Unfortunately, those experts have largely been correct about case rates post-PrEP in the United States so far.³³⁴

Public health agencies were also motivated to coordinate large-scale international clinical trials with safety and integrity. One of the ways the CDC engages in this costly process is to occasionally patent its clinical methods and to seek licensing partnerships for future clinical trials. The CDC helped conceived of (and pushed for) PrEP to prevent HIV infection and patented Truvada for PrEP against HIV during the PrEP global clinical trials. The CDC specifically patented the treatment of macaques for simian-analogue HIV while they were carrying out an experimental trial on Truvada for PrEP.³³⁵ The CDC's patent rights were later used (to no avail) as an enforcement tool in 2019 to push Gilead to provide more free supplies and services to communities

332. See *supra* Section IV.A.1.

333. See THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (containing at the 54-minute mark public health experts' brief opinion that PrEP was never intended to really bring the overall pandemic to a new low of transmission or case rates, but is still helpful for the vulnerable communities).

334. See Casey, *supra* note 1.

335. See *supra* Section III.C.2.c.

in need of PrEP via a high-stakes patent litigation brought by the CDC and Department of Justice.³³⁶

However, the health agencies and international philanthropies collaborating on these trials also have serious impediments to their work. Their funding is almost entirely from charitable donations, with some U.S. taxpayer assistance through the CDC and PEPFAR. Also, clinical trials routinely fail to show clinical effectiveness, as demonstrated in the Bill and Melinda Gates-sponsored trial of tenofovir-only as PrEP. These organizations must continually seek funding to support the high cost of this critical work—tens of millions of dollars for each of the major PrEP trials that lead to Truvada for PrEP.³³⁷

b) PrEP's Unique Commercialization Motives (Gilead)

From a commercialization perspective, Gilead accessed a much larger patient base with a drug to *prevent* HIV infection—gay men, people in sub-Saharan Africa, and other vulnerable community members who do *not* yet have HIV could take the drugs. This presented Gilead with a much greater profitability opportunity for its tenofovir-based products—to use them in otherwise healthy people.

Gilead was pressed by public health authorities, especially after the success of the iPrEx PrEP clinical trial in 2010, to pursue FDA approval of the PrEP indication.³³⁸ Offering discounted PrEP to communities in need would and has helped Gilead improve its image with its consumer bases. Yet, many in the communities vulnerable to HIV believe Gilead is not doing enough to expand access to PrEP to those who need it. A hotbed of AIDS activism kick-started CDC enforcement of Truvada for PrEP patents in 2019, largely due to Congressional hearings with Gilead and CDC scientists who worked on PrEP.³³⁹ Gilead won the enforcement patent litigation, but with HIV case rates persisting at about 30,000–40,000 annually in the United States, there is a strong argument that Gilead could be doing more to improve access to effective PrEP and educational resources to encourage its broader uptake in vulnerable communities.³⁴⁰

336. *See id.*

337. *See id.*

338. *See supra* Section III.C.2.a.

339. *See supra* Section III.C.2.c.

340. *See id.*

V. EPILOGUE

The HIV pandemic persists in 2023, with almost the same rate of new infections as since the availability of Truvada for PrEP in 2012: at least one every fifteen minutes.³⁴¹ Access to Truvada and its descendant medications for either treatment or PrEP indications has been slowed at least by: (1) stigma from outside and within the communities hit hardest by the pandemic; and (2) a Texas federal judge ruling in 2022 that the Affordable Care Act's mandatory coverage of PrEP medication infringes upon rights created by the Religious Freedom Restoration Act.³⁴² HIV/AIDS activists continue to raise alarms over the lack of affordable access and the need for improved education around sexual health in affected communities to further reduce the incidence of HIV and other STIs.³⁴³

Truvada, while imperfect, has greatly improved the lives for people either seeking treatment for HIV or prevention of HIV infection. The kidney and bone system toxicities associated with Truvada have been understood since its component drug, Viread, was associated with those same toxicities years before. Consumers of Truvada have brought many product liability lawsuits against Gilead based on these adverse effects.³⁴⁴ However, those with access to Truvada can protect themselves from HIV infection or, after infection, rapidly become “undetectable” to stave off AIDS for a normal lifetime. This is no small achievement when compared to the death sentence that HIV/AIDS was for tens of millions in the 1980s and early 1990s.³⁴⁵

Though Truvada was not a silver bullet to end HIV/AIDS, leaders in the AIDS innovation ecosystem did not expect it to be.³⁴⁶ Instead, Truvada and its

341. See COMMITTEE ON OVERSIGHT & ACCOUNTABILITY, *supra* note 222, at 11–13 (containing the statement of Dr. Lord to the committee).

342. *Braidwood Mgmt. Inc. v. Becerra*, No. 4:20-CV-00283-O, 2022 WL 4091215 (N.D. Tex. Sept. 7, 2022) (holding mandatory PrEP coverage by insurance per the Affordable Care Act to be a violation of the Religious Freedom Restoration Act).

343. See Rowland, *supra* note 216.

344. See, e.g., *Evans v. Gilead Scis., Inc.* (D. Hawaii, Aug. 31, 2020, No. 20-CV-00123-DKW-KJM) 2020 WL 5189995 (dismissing Truvada product liability claim citing effective warnings on labels based on clinical trial data); *but see Gaetano v. Gilead Scis., Inc.*, 529 F. Supp. 3d 333 (D.N.J. 2021) (denying motion to dismiss Truvada design defect tort claim for Gilead's failure to commercialize their known safer alternative drug design, the tenofovir prodrug called TAF now marketed as Descovy, instead of the tenofovir prodrug called TDF in Truvada).

345. See Shilts, *supra* note 7, at 496.

346. See THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (containing at the 54 minute mark public health experts' brief opinion that PrEP was never intended to really bring the overall pandemic to a new low of transmission or case rates, but is still helpful for the vulnerable communities).

component medicines have had an impressively positive impact on reducing the severity of the HIV/AIDS pandemic, especially in improving the lives of people living with HIV and helping to reduce the stigma associated with having the disabling illness by making PrEP available to at-risk communities.

Truvada represents decades of fundamental research, public policymaking, clinical experience, licensing, mergers and acquisitions, manufacturing, and marketing made possible by a uniquely large public-private coalition of individuals dedicated to a cause. The Truvada story illustrates how both private and public institutions can use the patent system, with all the rights and knowledge-sharing benefits it confers, to drive innovation forward towards more powerful medicines and methods of treatment. The uniquely intersectional AIDS innovation coalition certainly has a role to play in ending the HIV/AIDS pandemic once and for all.

VI. APPENDIX 1: TRUVADA SUMMARY TIMELINE

Year(s)	Key Events
1950s-70s	HIV circulates quietly in sub-Saharan Africa. ³⁴⁷
1978	In Europe, Holý and De Clercq synthesize DHPA, an antiviral with activity against herpes. DHPA was foundational to their development of tenofovir in the decade after. ³⁴⁸
1981	First U.S. hospitalizations and deaths due to mysterious disease (later known as AIDS) occur in Los Angeles. ³⁴⁹
1982	CDC initially names AIDS the “Gay-Related Immune Disorder,” contributing to lasting stigma. ³⁵⁰ Congress had appropriated, but the Reagan administration had not spent, \$8 million towards AIDS research grants. ³⁵¹
1983	Larry Kramer criticizes the U.S. government’s inaction on AIDS in his essay <i>1,112 and Counting</i> , helping to lead a grassroots movement of AIDS activism. ³⁵² French virologists Barré-Sinoussi and Montagnier isolate HIV, a novel retrovirus, from AIDS patients’ cells. ³⁵³

347. See Worobey et al., *supra* note 47, at 661–64.

348. See De Clercq et al., *supra* note 106, at 563–65.

349. See *A Timeline of HIV and AIDS*, *supra* note 44.

350. See Altman, *supra* note 233.

351. Kramer, *1,112 and Counting*, *supra* note 49.

352. See *id.*

353. See Barré-Sinoussi et al., *supra* note 8.

Year(s)	Key Events
1984	American scientists also isolate HIV from AIDS patients' cells, confirming the French virologists' findings and building consensus that HIV causes AIDS. ³⁵⁴
1985	In response to a reporter's question, President Reagan first publicly acknowledges the existence of AIDS. ³⁵⁵ Holý files his first European patent on a class of DHPA-derived nucleoside analogs that included PMPA, known now as "tenofovir." ³⁵⁶
1986	Holý files his U.S. patent on the class of DHPA derivatives that include PMPA, known now as "tenofovir." ³⁵⁷
1987	President Reagan gives his first speeches addressing HIV/AIDS, six years into the U.S. crisis, announcing executive orders and Congressional action ³⁵⁸ and settling a dispute among French and U.S. scientists over patent inventorship and ownership of HIV/AIDS test kits. ³⁵⁹ The FDA approves the first treatment for HIV/AIDS: AZT, which was originally created as a cancer treatment. ³⁶⁰ Bristol-Myers licenses Holý and De Clercq's DHPA derivatives for preclinical trials and drug development. ³⁶¹
1988	AIDS activist group ACT UP leader Larry Kramer writes <i>An Open Letter to Dr. Anthony Fauci</i> in the <i>San Francisco Examiner</i> , accusing Fauci of murder (and winning Fauci's attention). ³⁶² ACT UP storms the FDA headquarters in 1988 to demand acceleration of HIV/AIDS treatment R&D and approval. ³⁶³ President Reagan and Congress work together to create and fund the first federally legislated AIDS research programs, including the Institute for AIDS Research at NIH. ³⁶⁴

354. See Gallo et al., *supra* note 9; see also Levy et al., *supra* note 9.

355. Bennington-Castro, *supra* note 54.

356. See '716 Patent, *supra* note 110.

357. *Id.*; see also Antonín Holý 85 – *Story of tenofovir*, *supra* note 109.

358. See President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54.

359. See President Reagan's Remarks on AIDS Testing Patent Settlement, *supra* note 62.

360. See *Antiretroviral Drug Discovery and Development*, *supra* note 14.

361. See Antonín Holý 85 – *Story of tenofovir*, *supra* note 109.

362. See Kramer, *An Open Letter to Dr. Anthony Fauci*, *supra* note 90.

363. See Douglas Crimp, *supra* note 91.

364. See 42 U.S.C. § 300cc, *supra* note 11; see also President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54.

Year(s)	Key Events
1989	Squibb merges with Bristol-Myers to form Bristol-Myers Squibb, and the new company stops development of Holý and De Clercq's DHPA derivatives as well as other HIV antivirals. ³⁶⁵ Schinazi attends the Fifth International Conference on AIDS and observes a poster describing the synthesis of racemic 3TC, a compound with anti-HIV activity, and reports back to his Emory University colleague Liotta suggesting the synthesis can be improved. ³⁶⁶ The two begin research on 3TC synthesis.
1990	Activists with ACT UP storm the NIH, demanding more treatments brought to market than just AZT. ³⁶⁷
1991	Startup company Gilead Sciences, Inc., at recommendation of its recently hired Bristol-Myers alumnus Martin, licenses Holý and De Clercq's DHPA derivatives for drug development after the Bristol-Myers DHPA license lapsed in 1989. ³⁶⁸ Liotta and Schinazi file a patent on the method of synthesis and prodrug analogs of FTC, ³⁶⁹ later known as emtricitabine.
1992	The FDA announces the Accelerated Approval Program for small-molecule drugs that "fill an unmet," yet serious, "medical need"—primarily in response to AIDS activism. ³⁷⁰
1995	Gilead's simian trial of tenofovir is the first to demonstrate tenofovir's effectiveness in preventing HIV replication. ³⁷¹ Liotta and Schinazi file the composition and method of treatment patent on FTC, ³⁷² later known as emtricitabine. Glaxo purchases Burroughs-Wellcome—the pharma company that Liotta's team had licensed emtricitabine development rights to in the 1992–94 timeframe—laying off thousands of workers and abandoning its emtricitabine clinical development and IND application in the process. ³⁷³
1996	Burroughs-Wellcome HIV team leader Barry leaves Glaxo-Wellcome to found Triangle which licenses anew Liotta and company's emtricitabine for clinical development. ³⁷⁴

365. See *Antonín Holý 85 – Story of tenofovir*, *supra* note 109.

366. See Liotta & Painter, *supra* note 138, at 2092.

367. See *A Timeline of HIV and AIDS*, *supra* note 22.

368. See FORBES, *supra* note 119; see also John C. Martin, *supra* note 121.

369. See '085 Patent, *supra* note 148.

370. See AVALERE, *supra* note 95.

371. See Tsai et al., *supra* note 122.

372. U.S. Patent No. 6,642,245 B1 (filed June 7, 1995) (assigned to Emory University).

373. See Liotta & Painter, *supra* note 138, at 2095.

374. See *id.*

Year(s)	Key Events
	UNAIDS, the UN's strategic response organization for AIDS, launches to assist the growing scale of the pandemic in developing countries. ³⁷⁵
1997	Gilead's years of prodrug development for tenofovir pay off with the identification of an effective prodrug, tenofovir disoproxil fumarate (TDF), from preclinical studies in dogs. ³⁷⁶ Triangle submits a renewed IND for emtricitabine. ³⁷⁷
1998	Emtricitabine receives "Fast Track" status with the FDA. ³⁷⁸ Gilead publishes clinical study results showing tenofovir's effectiveness in treating HIV in humans. ³⁷⁹
2000	The 2000 International AIDS Conference is contentious, as developing nations, especially those in sub-Saharan Africa, plead with wealthy nations and aid organizations for help with the growing HIV/AIDS crisis in their nations. ³⁸⁰
2001	The WTO adopts the Doha Declaration on TRIPS and Public Health, providing for WTO member states the right issue compulsory licenses for "national emergencies" and other "urgent" circumstances. ³⁸¹ The FDA approves Gilead's TDF under the trade name Viread, just six months after Gilead filed the New Drug Application, under the Accelerated Approval Program. ³⁸²
2002	Triangle submits its New Drug Application to the FDA for emtricitabine to treat HIV, the same year Emory settled patent litigation over disputed inventorship, ownership, and infringement of the same drug. ³⁸³ After Triangle founder Barry died in early 2002, Gilead in December 2002 offered to purchase Triangle, primarily to build a combination therapy of tenofovir and emtricitabine. ³⁸⁴
2003	Gilead secures FDA approval for emtricitabine with the trade name Emtriva, having maintained the "Fast Track"-status New Drug Application that Triangle started the year before. ³⁸⁵

375. See UNAIDS, *supra* note 81.

376. See Shaw et al., *supra* note 126.

377. See Liotta & Painter, *supra* note 138, at 2095.

378. See *id.*

379. See Deeks et al., *supra* note 107.

380. See THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (describing at the thirty minute mark rationale for creation of the Global Fund and PEPFAR).

381. See DOHA DECLARATIONS, *supra* note 84, at 24–25.

382. See *Drug Approval Package: VIREAD® (Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 130.

383. See Liotta & Painter, *supra* note 138, at 2096.

384. See Alton, *supra* note 175.

385. See *Drug Approval Package: Emtriva® (emtricitabine) 200 mg Tablets*, *supra* note 179.

Year(s)	Key Events
2004	Gilead completes New Drug Application paperwork and later that same year receives approval for Truvada, the combination HIV treatment of tenofovir disoproxil fumarate and emtricitabine. ³⁸⁶ President Bush creates PEPFAR to combat the HIV/AIDS pandemic by funding the equitable distribution of treatments to developing nations globally. ³⁸⁷ Gilead enters into the first MTA with the CDC to support the CDC's clinical trials of Truvada for PrEP—Truvada consumed daily to <i>prevent</i> HIV infection, not just treat it. ³⁸⁸
2005	Gilead fully purchases, instead of licenses, the patent rights to emtricitabine from Emory University for \$525 million. ³⁸⁹
2006	The CDC begins filing method of treatment patents on Truvada for PrEP using the findings of its clinical trials. ³⁹⁰
2010	The iPrEx clinical trial concludes and initially reports regular Truvada consumption is 92% effective at preventing the spread of HIV (the effectiveness is later found to be 99%). ³⁹¹
2011	Gilead files a Supplementary New Drug Application with the FDA for a new indication of Truvada: Truvada for PrEP. ³⁹²
2012	Gilead secures FDA approval for Truvada for PrEP. ³⁹³
2019	Congress holds hearings interrogating Gilead and HIV scientists about Truvada's slow uptake as PrEP, where Representative Ocasio-Cortez makes the case for the U.S. government to enforce the CDC's patents against Gilead. ³⁹⁴ The U.S. Department of Justice sues Gilead for infringement of the CDC's patents on Truvada for PrEP. ³⁹⁵
2023	A jury found invalid, and nevertheless that Gilead did not infringe, the CDC's patents. ³⁹⁶

386. See *Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 30.

387. See *A Timeline of HIV and AIDS*, *supra* note 48.

388. See *Gilead Scis., Inc. v. United States*, 155 Fed. Cl. 336, 339.

389. See *Emory Univ.*, *supra* note 177.

390. See '509 Patent, *supra* note 201.

391. See *Grant et al.*, *supra* note 204, at 2597.

392. See *Glazek*, *supra* note 207.

393. See *U.S. Food and Drug Administration Approves Gilead's Truvada® for Reducing the Risk of Acquiring HIV*, *supra* note 213.

394. See *House Committee on Oversight & Accountability*, *supra* note 220.

395. See *United States v. Gilead Scis., Inc.*, 2019 WL 5942984 (D. Del.) (Trial Pleading).

396. See *The Editorial Board*, *supra* note 228.