

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.,
Petitioner,

v.

THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES,
Patent Owner.

Case No. IPR2019-01455
Patent No. 9,937,191
Filed: January 31, 2007

PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

I.	MANDATORY NOTICES	1
A.	Real Party-In-Interest (§42.8(b)(1))	1
B.	Other Proceedings (§42.8(b)(2))	1
C.	Lead and Backup Lead Counsel (§42.8(b)(3)).....	1
D.	Service on Petitioner (§42.8(b)(4))	1
E.	Fee for Petition (§42.15(a)).....	2
II.	INTRODUCTION	3
III.	CERTIFICATION; PROPOSED GROUNDS	5
IV.	KNOWLEDGE IN THE FIELD BEFORE FEBRUARY 2005	6
A.	HIV Infections.....	6
B.	Antiretrovirals Target Different Phases of HIV’s Life Cycle.....	8
C.	Combination Antiretroviral Regimens.....	10
D.	Truvada and Its Properties.....	12
E.	HIV Chemoprophylaxis	15
V.	THE ’191 PATENT	16
A.	Person of Ordinary Skill in the Art	16
B.	Summary of the Disclosure	17
C.	Claim Construction.....	18
1.	Representative Claims	18
2.	Proposed Constructions	20

a.	“ <i>[P]rotecting a primate host from a self-replicating infection</i> ” (Claims 1-12) / “ <i>[I]nhibiting establishment of a...self-replicating infection</i> ” (Claims 13-19).....	20
b.	“ <i>[S]elf-replicating infection</i> ” (Claims 1 and 13).....	24
c.	“ <i>[P]rior to the exposure</i> ” / “ <i>prior to a potential exposure</i> ”	25
VI.	PRECISE REASONS FOR RELIEF REQUESTED.....	28
A.	Cal-PrEP and CDC-PEP Are Prior Art to the Claims.....	28
1.	Cal-PrEP (Ex. 1011)	28
2.	CDC-PEP (Ex. 1012).....	29
B.	Cal-PrEP and CDC-PEP Provide Enabling Descriptions	31
C.	Claims 1-19 Are Anticipated by Cal-PrEP	33
1.	Overview of Cal-PrEP	33
2.	Independent Claims 1 and 13.....	36
a.	Preambles.....	36
b.	“ <i>[S]electing</i> ” “ <i>a primate host not infected with the immunodeficiency retrovirus</i> ” [1] / “ <i>an uninfected human that does not have the self-replicating infection</i> ” [13].....	37
c.	“ <i>[A]dministering...a combination comprising: (i) a pharmaceutically effective amount of emtricitabine and (ii) a pharmaceutically effective amount of tenofovir or [TDF]</i> ” “ <i>prior to the exposure</i> ” [1] / “ <i>prior to a potential exposure</i> ” [13] “ <i>wherein the combination is administered orally in tablet form</i> ” [1] / “ <i>in a tablet</i> ” [13].....	37
d.	“ <i>Thereby</i> ” Clauses	42
3.	Claims 2-3	43
4.	Claims 4, 14, and 17	43

5.	Claim 5	44
6.	Claim 6	44
7.	Claims 7 and 16.....	44
8.	Claims 8, 12, and 18	45
9.	Claim 9	46
10.	Claims 10 and 19.....	47
11.	Claims 11 and 15.....	50
D.	Claims 1 to 19 Would Have Been Obvious	51
1.	Overview of CDC-PEP	52
2.	A Skilled Person Would Have Been Motivated to Commence Prophylaxis <i>Before</i> an Exposure Based on Cal-PrEP.....	58
3.	CDC-PEP and Cal-PrEP Both Recommended Truvada for Prophylaxis of HIV-Uninfected Individuals.....	63
4.	A Skilled Person Would Reasonably Expect PrEP Using Truvada to be Effective in Preventing HIV Infection	65
a.	Extensive Experiences with PEP Established a Reasonable Expectation of Success.....	66
b.	PrEP and PEP Regimens Have the Same Pharmacological Mechanism and Cause the Same Result	68
c.	Cal-PrEP Described Clinical Trials Focused on Decreasing Community Rates of HIV Infection	70
d.	HIV Chemoprophylaxis Was Not “Highly Unpredictable”	73
E.	There Are No Secondary Indicia of Non-Obviousness	76

**VII. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION
UNDER 35 U.S.C. §325(D)79**

VIII. CONCLUSION84

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Apotex Inc. v. Novartis AG</i> , IPR2017-00854, Paper 11 (P.T.A.B. July 18, 2017)	80
<i>Becton Dickinson & Co. v. B. Braun Melsungen AG</i> , IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017)	79
<i>Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.</i> , 246 F.3d 1368 (Fed. Cir. 2001)	21, 22, 32, 51
<i>In re Gleave</i> , 560 F.3d 1331 (Fed. Cir. 2009)	32
<i>Great W. Cas. Co. v. Transpacific IP I Ltd.</i> , IPR2015-01912, Paper 10 (P.T.A.B. Mar. 22, 2016)	6
<i>Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.</i> , 821 F.3d 1359 (Fed. Cir. 2016)	66
<i>Merck & Co. v. Teva Pharmaceuticals USA</i> , 395 F.3d 1364 (Fed. Cir. 2005)	78
<i>In re Montgomery</i> , 677 F.3d 1375 (Fed. Cir. 2012)	22
<i>Ormco Corp. v. Align Tech., Inc.</i> , 463 F.3d 1299 (Fed. Cir. 2006)	77
<i>Rasmusson v. SmithKline Beecham Corp.</i> , 413 F.3d 1318 (Fed. Cir. 2005)	32, 51
<i>SanDisk Corp. v. Kingston Tech. Co.</i> , 695 F.3d 1348 (Fed. Cir. 2012)	29
<i>Schering Corp. v. Geneva Pharms.</i> , 339 F.3d 1373 (Fed. Cir. 2003)	32

SkinMedica, Inc. v. Histogen Inc.,
727 F.3d 1187 (Fed. Cir. 2013)46, 47

Statutes

35 U.S.C. § 102(b)5
35 U.S.C. § 1035, 82
35 U.S.C. § 325(d)79, 80, 83, 84

Other Authorities

U.S. Patent & Trademark Ofc., Trial Practice Guide (July 2019
Update), 84 Fed. Reg. 33,925 (July 16, 2019).....79, 80

I. MANDATORY NOTICES

A. Real Party-In-Interest (§42.8(b)(1))

The real party-in-interest is Gilead Sciences, Inc., located at 333 Lakeside Drive, Foster City, California 94404.

B. Other Proceedings (§42.8(b)(2))

U.S. Patent No. 9,937,191 (Ex. 1005) (“’191 Patent”) is not the subject of any other proceeding.

Petitioner has filed *inter partes* review petitions against three patents issued from applications claiming priority to the application from which the ’191 Patent issued; namely: (i) IPR2019-01453 (challenging U.S. Patent No. 9,044,509) (ii) IPR2019-01454 (challenging U.S. Patent No. 9,579,333); and (iii) IPR2019-01456 (challenging U.S. Patent No. 10,335,423).

C. Lead and Backup Lead Counsel (§42.8(b)(3))

<u>Lead Counsel</u> Jeffrey P. Kushan Reg. No. 43,401 jkushan@sidley.com 202-736-8914	<u>Backup Lead Counsel</u> Lauren Cranford Katzeff Reg. No. 67,499 lkatzeff@sidley.com 202-736-8176
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D. Service on Petitioner (§42.8(b)(4))

Service may be made by e-mail (IPRNotices@sidley.com) or by mail or hand delivery to: Sidley Austin LLP, 1501 K Street, N.W., Washington, D.C. 20005. The fax number for Counsel is 202-736-8711.

E. Fee for Petition (§42.15(a))

The Director is authorized to charge the fee specified by 37 CFR §42.15(a) to Deposit Account No. 50-1597.

II. INTRODUCTION

Since the 1990s, it has been standard practice to administer combinations of antiretroviral agents to prevent human immunodeficiency virus (“HIV”) infections in uninfected individuals who have been exposed to the virus, a regimen termed post-exposure prophylaxis (“PEP”). By 2005, PEP regimens had evolved to use newer antiretrovirals, particularly Petitioner Gilead’s Truvada®, a once-daily oral formulation of tenofovir disoproxil fumarate (“TDF”) plus emtricitabine (“FTC”). Indeed, shortly after it became available, the Centers for Disease Control and Prevention (CDC)¹ updated their widely-followed PEP guidelines (“CDC-PEP”)² to specify use of Truvada (i.e., TDF+FTC) as one of two “preferred” “backbone” regimens to prevent HIV infection after exposure.

In 2004, two California-based HIV/AIDS organizations³ published a report (“Cal-PrEP”) describing an extension of the PEP regimen for “certain people at

¹ The CDC is an agency of the Department of Health & Human Services (HHS), the Patent Owner.

² Ex. 1012 (“CDC-PEP”), 20.

³ The Center for HIV Identification, Prevention, and Treatment Services and AIDS Partnership California. *See* Ex. 1001 (“Cal-PrEP”), 2-3.

high risk of HIV infection”⁴—those who engage in conduct that repeatedly exposes them to HIV. Their regimen specified giving high-risk individuals antiretrovirals (particularly Truvada) before they are exposed to HIV (“pre-exposure prophylaxis” or “PrEP”), rather than after (“PEP”). Cal-PrEP justified this regimen by reasoning that any potential side-effects of using antiretrovirals for extended periods would be far outweighed by preventing infection of the high-risk individual on PrEP, and, by extension, others in that person’s community who might become exposed to HIV via that high-risk individual.

The claims of the ’191 Patent encompass the PrEP regimen taught by Cal-PrEP—administering Truvada (TDF+FTC) before an HIV exposure to prevent an HIV infection. The ’191 Patent claims are thus anticipated by Cal-PrEP. The ’191 Patent claims also are an obvious variation of the guidance in CDC-PEP when it is considered with the recommendations in Cal-PrEP to administer antiretrovirals (including Truvada) to “high-risk” individuals before actual or potential HIV exposures. Petitioner respectfully requests the Board to institute *inter partes* review of Claims 1-19 of the ’191 Patent and cancel these claims.

⁴ Cal-PrEP, 3.

III. CERTIFICATION; PROPOSED GROUNDS

Gilead Sciences, Inc. certifies it is not barred or estopped from requesting *inter partes* review of the '191 Patent. Neither Gilead, nor any party in privity with Gilead, has (i) filed a civil action challenging the validity of any claim of the '191 Patent; or (ii) been served a complaint alleging infringement of the '191 Patent more than a year prior to the present date. The '191 Patent also has not been the subject of a prior *inter partes* review. Gilead certifies that the '191 Patent is available for *inter partes* review.

Petitioner proposes two grounds:

- (i) anticipation of Claims 1-19 by Cal-PrEP under 35 U.S.C. §102(b);
and
- (ii) obviousness of Claims 1-19 over CDC-PEP in view of Cal-PrEP under 35 U.S.C. §103.

Petitioner submits these grounds are not redundant. The anticipation ground is not redundant with the proposed obviousness ground because the latter rests on a different rationale for unpatentability and is presented to respond to potential arguments Patent Owner may make regarding what Cal-PrEP teaches. And

because both grounds share a prior art reference and the knowledge held by the skilled person, they are “rational, narrowly targeted, and not burdensome.”⁵

IV. KNOWLEDGE IN THE FIELD BEFORE FEBRUARY 2005

What the skilled person knew at the time of an invention is integral to the assessment of patentability. Here, the critical date is February 3, 2005—one year before the earliest priority date claimed by the '191 Patent. The skilled person's knowledge of HIV, antiretroviral agents and strategies for treatment and prophylaxis of HIV by that date was extensive.

A. HIV Infections

The human immunodeficiency virus (HIV) targets and destroys the immune system's CD4+ cells, which impedes the body's ability to fight infections and illnesses and eventually progresses to acquired immune deficiency syndrome (“AIDS”).⁶ HIV is a retrovirus and exists outside of cells as viral particles (“virions”) (Figure)⁷:

⁵ *Great W. Cas. Co. v. Transpacific IP I Ltd.*, IPR2015-01912, Paper 10, 17-18 (P.T.A.B. Mar. 22, 2016).

⁶ *See, e.g.*, Ex. 1138 (“Janeway”), 451-57; Ex. 1147 (“Cohen-1999”), 1458-59, 1474-76.

⁷ Ex. 1148 (“Gelderblom-1991”), 620.

proteins, package them together with HIV RNA and release them from the HIV-infected cell as new virions.

The CD4+ cells transformed by the initial exposure to HIV are called “founder” cells,¹⁰ which rapidly begin producing virions that can infect other CD4+ cells.¹¹ The body’s immune system targets and removes the founder cells and other CD4+ cells transformed by HIV, but at some point (approximately three days after the exposure) the volume of new virions and infected CD4+ cells overwhelms the host’s immune system.¹² At that point, the HIV infection was considered established.¹³

B. Antiretrovirals Target Different Phases of HIV’s Life Cycle

Antiretroviral drugs inhibit replication of HIV viral RNA in CD4+ cells and production of new virions, which prevents additional CD4+ cells from being

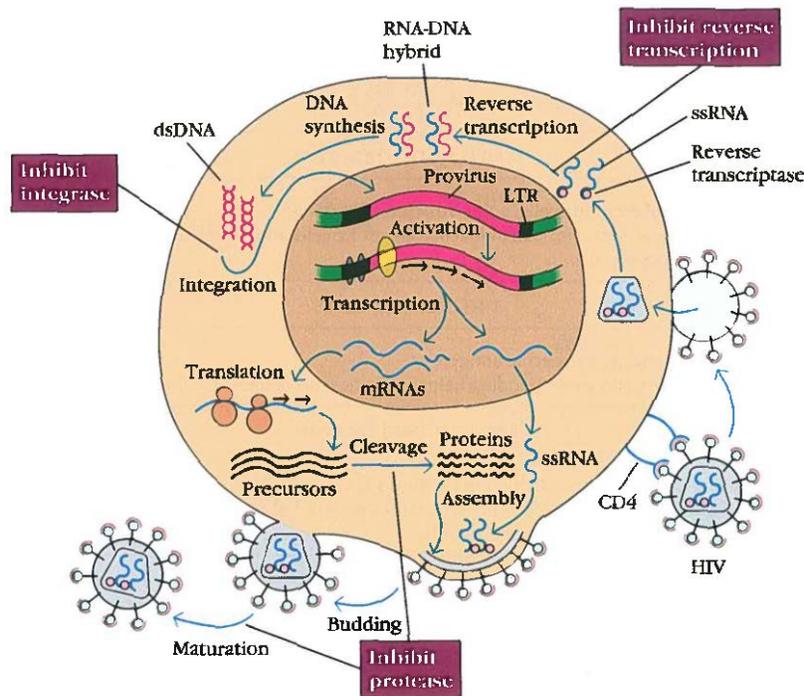
¹⁰ Ex. 1061 (“Haase-2005”), 784; Ex. 1137 (“Miller”), 9217.

¹¹ Haase-2005, 784.

¹² Youle-Decl. ¶73; Haase-2005, 784; Ex. 1156 (“Tsai-1998”), 4271 (“...short temporal window during which...treatment can block establishment of persistent infection”); Ex. 1157 (“Lifson”), 2584; Ex. 1013 (“CDC-May1998”), 5.

¹³ Youle-Decl. ¶73; Haase-2005, 784, 787; Miller, 9225-26.

transformed by HIV.¹⁴ Different classes of antiretroviral drugs were known to target different phases of HIV's life cycle (Figure).¹⁵



Agents that prevent HIV viral DNA from being created or integrated into the host cell's DNA are the most effective antiretroviral agents.¹⁶ Reverse transcriptase inhibitors ("RTIs") are particularly effective because they prevent

¹⁴ Janeway, 458-59.

¹⁵ Goldsby, 451-53; Janeway, 458-59; Lifson, 2584; Ex. 1015 ("Hu"), 6087.

¹⁶ Cal-PrEP, 11.

creation of the HIV proviral cDNA.¹⁷ Two examples of RTIs are nucleotide reverse transcriptase inhibitors (“NtRTIs”) such as tenofovir and tenofovir disoproxil fumarate (TDF)¹⁸ and nucleoside reverse transcriptase inhibitors (“NRTIs”) such as emtricitabine (FTC).¹⁹

C. Combination Antiretroviral Regimens

Since the 1990s, it was known that the most effective way to “accomplish durable suppression of HIV replication” is to administer two or more different antiretroviral drugs (“combination” therapy)—one agent (“monotherapy”) does not

¹⁷ See Goldsby, 451-52; Ex. 1021 (“Barreiro”), 234; Youle-Decl. ¶95.

¹⁸ “TDF is a prodrug of tenofovir.” Cal-PrEP, 8; see also Youle-Decl. ¶81; Ex. 1029 (“De-Clercq-JCV”), 118-19.

¹⁹ Ex. 1025 (“Truvada®-Label”), 2-3; Ex. 1016 (“De-Clercq-IJB”), 1806-10; De-Clercq-JCV, 115-18; Ex. 1030 (“Bang”), 2413-15; see also Youle-Decl. ¶¶78-80, 96. A third type of RTI—non-nucleoside reverse transcriptase inhibitors (“NNRTIs”)—binds to reverse transcriptase and inhibits its functions. See Ex. 1067 (“Saag”), 26; De-Clercq-JCV, 118; Goldsby, 451-53; Youle-Decl. ¶83.

ensure sufficient and sustainable suppression.²⁰ Monotherapy also risks creating drug resistance if HIV mutates to overcome the inhibition of viral replication.²¹ Combination therapy minimizes that risk as it requires HIV to acquire multiple mutations to overcome the inhibitory effect of the drugs.²²

The CDC thus has recommended combination therapy for both treatment and prophylaxis of HIV since well before 2005, particularly two NRTIs²³ plus either a protease inhibitor (PI) or an NNRTI.²⁴ The two NRTIs are referred to as

²⁰ Ex. 1014 (“CDC-ARV”), 10-11; Ex. 1017 (“Bassett”), 396; Youle-Decl. ¶¶86-87, 223.

²¹ CDC-ARV, 10; Ex. 1018 (“Coffin”), 487-88; Cal-PrEP, 11 (discussing susceptibility of TDF monotherapy to prevalent K65R mutation).

²² CDC-ARV, 10; Ex. 1019 (“Hammer”), 731; Ex. 1020 (“Gulick”), 738.

²³ NtRTIs and NRTIs are sometimes referred to generally as “NRTIs.” Youle-Decl. ¶79.

²⁴ CDC-ARV, 11 (treatment); CDC-May1998, 8-9; *see also* Ex. 1024 (“CDC-2001”), 24-27 (prophylaxis); *see also* Barreiro, 234, Youle-Decl. ¶117.

the “backbone” of the combination regimen.²⁵ TDF+FTC is an example of a two-NRTI backbone.²⁶

D. Truvada and Its Properties

The FDA approved Truvada in August 2004 as a once-daily oral formulation of two agents, TDF+FTC, for treating HIV infection in combination with a third agent.²⁷ Truvada contains 300 mg of TDF and 200 mg of FTC, the same doses in Gilead’s single-agent formulations of FTC (Emtriva®) and TDF (Viread®).²⁸

In October 2004, zidovudine+lamivudine (Combivir®) was the prevailing backbone and when combined with efavirenz was considered “one of the most effective, thoroughly investigated, and well-tolerated regimens for the treatment of antiretroviral-naïve patients.”²⁹ Truvada’s clinical results, however, established that TDF+FTC caused fewer side-effects than Combivir (8% versus 15%) with

²⁵ Youle-Decl. ¶88.

²⁶ Ex. 1022 (“Collins”), 1, Title; Youle-Decl. ¶89.

²⁷ Truvada®-Label, 21; Ex. 1026 (“Approval-Letter”), 1, 6.

²⁸ Truvada®-Label, 1; Ex. 1027 (“Viread®-Label”), xv; Ex. 1028 (“Emtriva®-Label”), 17.

²⁹ Ex. 1034 (“DeJesus”), 1038.

comparable efficacy.³⁰ Truvada also avoided the K65R mutation seen with TDF monotherapy.³¹

Within months of its approval, skilled persons recognized Truvada's advantages over other antiretroviral combinations:

- TDF+FTC provides synergistic antiretroviral activity relative to the activity exhibited by each agent alone.³²
- TDF+FTC avoids mutual interference (when two agents compete for the same natural nucleotide/nucleoside), which decreases antiretroviral activity and increases rates of adverse events and drug-related toxicities.³³

³⁰ Ex. 1035 (“Moyer”), 3 (fewer instances of anemia, neutropenia, diarrhea, fatigue, and depression in TDF+FTC-arm patients).

³¹ *Id.* 2-3; *see also* Ex. 1039 (“Brenner”), F12; Youle-Decl. ¶101.

³² Truvada®-Label, 3; Ex. 1031 (“Vela”), Conclusions; Ex. 1032 (“Dando”), 2076; Youle-Decl. ¶¶97, 204.

³³ Barreiro, 234, 236; Youle-Decl. ¶98.

- TDF+FTC have symmetric pharmacokinetic properties³⁴— a sufficiently long half-life to be suitable for once-daily dosing and no harmful interactions, which enables Truvada to provide prolonged exposure with less frequent dosing.³⁵

Truvada was “an important step forward”³⁶ because its once-a-day fixed-dose tablet formulation “simplif[ies] treatment regimens by reducing the number of pills and times per day patients need to take them”³⁷ “enhanc[ing] therapy adherence, and thus, the likelihood of further improvement in the success rate.”³⁸ Truvada also demonstrated superior safety,³⁹ a particularly important feature for patients using antiretrovirals for extended periods in HIV prophylaxis or who were antiretroviral-naïve.⁴⁰ Experts accurately predicted Truvada would “soon be the

³⁴ Ex. 1033 (“Back”), S3-S4; Youle-Decl. ¶104.

³⁵ Back, S2-S4; Barreiro, 235; Youle-Decl. ¶¶103-04.

³⁶ Ex. 1041 (“De-Clercq-2005”), 265.

³⁷ Ex. 1040 (“FDA-2004”), 2 (quoting Acting FDA Commissioner).

³⁸ De-Clercq-2005, 265.

³⁹ Barreiro, 238; Youle-Decl. ¶98.

⁴⁰ Cal-PrEP, 11; CDC-ARV, 47-48; CDC-May1998, 9.

starting treatment of choice for drug-naïve HIV patients”⁴¹ and called it “a truly recommendable drug regimen for the treatment of antiretroviral-naïve patients.”⁴²

Consequently, by 2005, a skilled person would have considered Truvada (TDF+FTC) to be a preferred option for both HIV treatment and prophylaxis.⁴³

E. HIV Chemoprophylaxis

Before February 2005, combination antiretroviral prophylaxis (including with TDF+FTC) of HIV-uninfected individuals exposed to HIV was well-established.⁴⁴ PEP was known to effectively prevent HIV infection in settings including: (i) HIV/AIDS caregivers exposed via accidental needle-sticks; (ii) uninfected infants with HIV-positive mothers exposed during childbirth or through breastfeeding; (iii) individuals engaging in unprotected sex with an infected partner; (iv) intravenous drug users; and (v) sex workers.⁴⁵

⁴¹ Moyer, 3.

⁴² De-Clercq-2005, 250.

⁴³ Youle-Decl. ¶¶103, 163, 230.

⁴⁴ CDC-PEP, 8-9; Ex. 1042 (“Youle-JIAPAC”), 103-04; Ex. 1043 (“Gayle”), 4-5; Ex. 1044 (“Chase”), 2.

⁴⁵ Youle-Decl. ¶¶111-14.

PEP regimens maintain a persistent concentration of antiretrovirals in the patient, which suppresses the CD4+ cell-mediated replication of HIV after an exposure and thereby prevents establishment of the infection.⁴⁶ Before 2005, single-agent TDF-based regimens showed protective effects in animal testing, which reinforced the viability of using TDF in HIV prophylaxis.⁴⁷ And within months of Truvada's approval in 2004, guidelines from CDC and others endorsed it as a preferred agent for both post- and pre-exposure HIV prophylaxis.⁴⁸

V. THE '191 PATENT

A. Person of Ordinary Skill in the Art

A person of ordinary skill in the art (“skilled person”) would have been an individual familiar with treatment and prophylaxis of HIV or similar viruses in individuals in a clinical and/or pre-clinical setting. The knowledge held by such a person would have resulted from that person's education, training and experience,

⁴⁶ *Id.* ¶122; Janeway 458-59.

⁴⁷ Tsai-1998, 4265, 4271 (calling TDF “PMPA,” *see* Youle-Decl. ¶81); Ex. 1045 (“Tsai-1995”), 1197, 1199 (same); Ex. 1046 (“Van Rompay-1998”), F81; Ex. 1047 (“Otten-2004”), 9772-74; Lifson, 2584, 2589.

⁴⁸ CDC-PEP, 8-10; Cal-PrEP, 11.

which would have included, for example, either an M.D. or an advanced degree in an allied field (e.g., microbiology, epidemiology, public health), along with 2-3 years of experience in those fields or in treating patients.⁴⁹

B. Summary of the Disclosure

The '191 Patent concerns methods for chemoprophylaxis of primate immune deficiency viruses by administering a “combination of antiretroviral agents.”⁵⁰ It suggests that “if the establishment of a retroviral could be blocked before the HIV burden expands into a self-propagating infection, an individual could avoid contraction of HIV.”⁵¹ The '191 Patent identifies known antiretrovirals used in highly active antiretroviral therapy (HAART) for use in its regimen, including NRTI and NtRTI formulations,⁵² and notes an “exemplary NtRTI prodrug” is

⁴⁹ Youle-Decl. ¶16.

⁵⁰ '191 Patent, 3:16.

⁵¹ *Id.* 1:49-51.

⁵² *See, e.g., id.* 5:24-28 (“With conventional NRTI and NtRTI formulations, currently approved for HAART...”); *id.* 5:63-6:3 (NRTIs); *id.* 6:4-:12 (NtRTIs); *supra* §IV.B.

tenofovir disoproxil fumarate (TDF).”⁵³ It also indicates that subjects can be given any of a wide variety of other known antiretrovirals.⁵⁴

The ’191 Patent describes experiments in which macaques (primates) were given small doses of an engineered form of the simian immunodeficiency virus (SIV) containing components of HIV.⁵⁵ By February 2005, this was a well-known model for testing antiretroviral drugs for HIV prophylaxis.⁵⁶ The experimental results showed varying degrees of protection against infection.⁵⁷

C. Claim Construction

1. Representative Claims

Claims 1 and 13 are the independent claims; each defines a method with the same two operative steps:

- (a) selecting an uninfected primate host or an uninfected human (i.e., “a primate host not infected with the immunodeficiency retrovirus”

⁵³ ’191 Patent, 4:64-67; 1:60-64.

⁵⁴ *Id.* 6:13-16.

⁵⁵ *Id.* 7:64-8:10.

⁵⁶ *See, e.g.*, Otten-2004, 164; Ex. 1048 (“Li”), 639; Youle-Decl. ¶¶211, 50.

⁵⁷ ’191 Patent, 9:38-10:12.

(Claim 1) or “an uninfected human that does not have the self-replicating infection” (Claim 13)) and

- (b) administering to that subject “a combination comprising: (i) a pharmaceutically effective amount of emtricitabine [FTC] and (ii) a pharmaceutically effective amount of tenofovir” “or tenofovir disoproxil fumarate [TDF]” (Claims 1 and 13).

Claim 1 specifies that the combination is administered “orally in tablet form” while Claim 13 specifies that each of TDF and FTC is administered “in a tablet.”

Despite having identical operative steps, the objective and desired results of the claimed methods are expressed in different terms:

<i>Claim 1</i>	<i>Claim 13</i>
A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:	A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:
[operative steps]	[operative steps, including administration of each of TDF and FTC “in a tablet”]

<p>wherein the combination is <u>administered orally in tablet form prior to the exposure</u> of the primate host to the immunodeficiency retrovirus,</p>	
<p>thereby protecting the primate host from infection with the immunodeficiency retrovirus.</p>	<p>thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered <u>prior to a potential exposure</u> of the human to the human immunodeficiency retrovirus.</p>

2. Proposed Constructions

With four exceptions, the terms used in the claims require no interpretation.

- a. “[P]rotecting a primate host from a self-replicating infection” (Claims 1-12) / “[I]nhibiting establishment of a...self-replicating infection” (Claims 13-19)

The preamble of Claim 1 specifies “[a] process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus,” while that of Claim 13 specifies “[a] process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human.” Both repeat the substance of their preambles after reciting their “selecting” and “administering” steps; Claim 1 states “thereby protecting the primate host from infection with the immunodeficiency retrovirus” while Claim 13

states “*thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human....*”

A preamble is not limiting if “the body of the claim sets out the complete invention, and the preamble is not necessary to give ‘life, meaning and vitality’ to the claim.”⁵⁸ Also, claim language specifying the result of performing a therapeutic method is routinely found to not require that outcome in every patient, but is only the desired result of treatment.⁵⁹ And simply reciting what inherently results from performing the steps of a known therapeutic method cannot render novel a claim specifying those same steps.⁶⁰

Here, the preambles of Claims 1 and 13 do not alter how the operative steps of each claimed method are to be performed. Instead, the “selection” and “administration” steps in each claim define the complete process. Reciting the results of performing these operative steps in “thereby” clauses likewise does not limit the scope of these claims.

⁵⁸ *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1373-74 (Fed. Cir. 2001).

⁵⁹ *See, e.g., id.* 1375-76.

⁶⁰ *See, e.g., In re Montgomery*, 677 F.3d 1375, 1381-82 (Fed. Cir. 2012).

The specification reinforces these conclusions. For example, it states that “‘protection’ as used in the context of a host primate response to an immunodeficiency virus [HIV] challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.”⁶¹ The specification, however, does not suggest these tests alter how the operative steps of the method are to be performed. Instead, it suggests that “protection” results from administering any combination of an NRTI and an NtRTI.⁶² Moreover, the specification indicates that known FDA-approved antiretroviral agents are to be used as is—it does not suggest altering the dose of the agents, or using a unique pattern of administration.⁶³ Given that the

⁶¹ ’191 Patent, 4:11-15. A host is “serologically negative” if the quantity of antiviral antibodies in a sample from the host is lower than a threshold value indicative of a “negative” result. Youle-Decl. ¶166. A negative response in PCR testing for the viral genome is when the quantity of viral DNA in a sample from the host is below a value indicative of a “negative” result. *Id.* ¶¶166-67.

⁶² ’191 Patent, 2:16-21; 4:35-67, 5:63-6:12.

⁶³ *Id.* 6:28-49.

degree of viral suppression of these different agents varies widely,⁶⁴ and that the experimental examples show varying degrees of protection for even a subset of those agents,⁶⁵ “protection” must necessarily encompass a range of outcomes.

The same conclusion holds for “inhibiting establishment.” The specification nowhere defines or uses this phrase. Instead, it portrays “establishment” as the stage of progression of the HIV infection when it becomes “a self-propagating” or “self-replicating retroviral” infection.⁶⁶ None of its passages addressing “establishment” proposes altering the performance of the operative steps of Claim 13, and the specification reports varying degrees of success in preventing establishment of infections.⁶⁷ “Inhibiting establishment” thus does not require success in every individual, but is simply identifying the objective of the method.

⁶⁴ See Youle-Decl. ¶¶85, 88, 101.

⁶⁵ See, e.g., '191 Patent, 9:49-51 (“Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed.”) (emphasis added).

⁶⁶ *Id.* 1:49-51 (“self-propagating”), 5:1-5 (“self-replicating”); see also *id.* 1:22-23.

⁶⁷ See, e.g., *id.* 9:49-51; footnote 64, *supra*.

Consequently, the preamble and “thereby” clauses in Claims 1 and 13 are non-limiting—each specifies only an intended result of the process; neither requires 100% inhibition or prevention in any particular individual.

b. “[S]elf-replicating infection” (Claims 1 and 13)

All the claims use the phrase “self-replicating infection.”⁶⁸ There is no express definition of this phrase in the patent disclosure, and it does not have a uniform scientific meaning.⁶⁹

As used in the specification, “self-replicating infection” refers to a point in time after an HIV exposure when the body’s immune system alone cannot prevent progression of the HIV infection.⁷⁰ That was known to occur about three days (~72 hours) after an exposure, which corresponds to when infected CD4+ cells are

⁶⁸ If the Board determines the preambles and “thereby” clauses are not limiting, it need not construe “self-replicating infection.”

⁶⁹ HIV does not “self-replicate”—it enters cells and induces them to produce additional copies of HIV virions. *See supra* §IV.A.

⁷⁰ Youle-Decl. ¶¶187-88.

being produced faster than the immune system can destroy them.⁷¹ Consistent with this, the '191 Patent identifies the transition to a self-replicating infection as occurring “within a few days” and explains at that point HIV virions are “self-replicating into a retroviral titer detectable in host blood serum.”⁷²

A “*self-replicating infection*” thus means “*an HIV infection that can no longer be suppressed solely by the host’s immune system.*”

c. “[P]rior to the exposure” / “prior to a potential exposure”

The claims use a variety of phrases (or none) to specify when a combination of an NRTI and an NtRTI is to be administered relative to an “exposure”:

- Independent Claim 1 specifies administration is “prior to the exposure”;
- Independent Claim 13 specifies administration is “prior to a potential exposure”; and
- Claims 10 and 19 specify that administration is “daily for several days, weeks or months both before and after an exposure.”

⁷¹ See, e.g., Haase-2005, 783-84; Ex. 1065 (“Fauci-1996”), 654; CDC-PEP, 8 (recommending treatment within 72 hours of exposure); Youle-Decl. ¶¶53-54.

⁷² '191 Patent, 1:45-49.

The '191 Patent uses “exposure” to refer to HIV viral particles being introduced into an individual in a manner that can result in infection.⁷³

The '191 Patent recognizes that certain populations of individuals will experience repeated exposures to HIV, observing that prophylaxis is “particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure.”⁷⁴ The '191 Patent thus recognizes what was well known in 2005—that certain “high risk” populations of uninfected individuals engage in activities that cause them to be repeatedly exposed to HIV over a defined period.⁷⁵

The '191 Patent also recognizes that the primary benefit of PrEP is to reduce the rate of new HIV infections in a community, explaining it provides an “epidemiological advantage...in controlling the outbreak and spread of a retrovirus within a population” when provided “prophylactically to high-risk persons such as sex workers....”⁷⁶ The skilled person would recognize this epidemiological goal

⁷³ *Id.* 3:20-27, 31-35.

⁷⁴ *Id.* 5:31-35 (emphasis added).

⁷⁵ Cal-PrEP, 1; Youle-Decl. ¶144.

⁷⁶ '191 Patent, 5:51-56 (emphasis added).

may not be realized even though the regimen will prevent HIV infection in an individual who follows it.⁷⁷

The '191 Patent also distinguishes “the exposure” from the “first exposure” of the uninfected individual to HIV—only the first HIV exposure is the “initial exposure.”⁷⁸ None of the claims uses the terms “initial” or “first” or otherwise requires agents to be administered before the first/initial “exposure.” Instead, they use the words “the exposure” or “a potential exposure,” thus indicating administration of antiretroviral agents can occur after an earlier HIV exposure, as long as (i) the earlier exposure did not result in an HIV infection (i.e., the individual remains “uninfected”), and (ii) administration occurs before a future exposure.

Claims 13 specifies administration of the combination prior to a “potential” exposure. The ordinary meaning of “potential” is that an event may, but may not necessarily, occur.⁷⁹ Claim 13, thus, does not require an HIV exposure to actually

⁷⁷ Youle-Decl. ¶¶106-07, 253.

⁷⁸ *See, e.g.*, '191 Patent, 2:2-5; 3:37-40.

⁷⁹ Ex. 1122 (“Random House Dictionary”), 1514 (defining “potential” as “possible, as opposed to actual”).

occur after administration of the antiretroviral agents, which aligns with the method being prophylactic in nature.

Consequently, each of Claims 1 and 13 encompasses a process whereby at least one NRTI and one NtRTI are administered after an HIV exposure of the individual that did not result in an infection. Moreover, only Claims 1, 10, and 19 affirmatively require an administration to precede an actual HIV exposure, with Claims 10 and 19 additionally requiring an administration after an exposure.⁸⁰

VI. PRECISE REASONS FOR RELIEF REQUESTED

A. Cal-PrEP and CDC-PEP Are Prior Art to the Claims

The '191 Patent claims priority to provisional application 60/764,811, filed February 3, 2006. The prior art used in the grounds (Cal-PrEP and CDC-PEP) was published more than a year prior to that date (i.e., before February 3, 2005).

1. Cal-PrEP (Ex. 1011)

Cal-PrEP bears a publication date of November 2004.⁸¹ A December 8, 2004 archive of the website “www.aidspartnershipca.com” provides access to the

⁸⁰ See *SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1360 (Fed. Cir. 2012).

⁸¹ Cal-PrEP, 2.

Cal-PrEP document,⁸² and archived pages of that website announced Cal-PrEP's availability as early as November 30, 2004.⁸³ Archives of another website (www.uclaisap.org) as early as December 21, 2004 likewise provide access to the Cal-PrEP document⁸⁴ and announced Cal-PrEP's availability by November 28, 2004.⁸⁵ The Cal-PrEP authors also testified that Cal-PrEP was disseminated to the public starting in November 2004.⁸⁶

2. CDC-PEP (Ex. 1012)

CDC-PEP was published on January 21, 2005 in Volume 54, No. RR-2 of the CDC periodical Morbidity and Mortality Weekly Report Recommendations and Reports (MMWR-RR) on January 21, 2005.⁸⁷ MMWR-RR has been an

⁸² Ex. 1108 (“Wayback-Decl.”), 6-46.

⁸³ See Ex. 1126; see also Ex. 1127.

⁸⁴ Wayback-Decl., 47-87.

⁸⁵ *Id.* 170-71.

⁸⁶ Ex. 1103 (“Szekeres-Decl.”) ¶5; Ex. 1129 (“Coates-Decl.”) ¶10.

⁸⁷ Cal-PrEP, cover-1.

official “report[] to CDC by state health departments” since prior to 1990.⁸⁸

MMWR-RR issues are published by CDC’s Coordinating Center for Health Information and Service, “officially released to the public” and “available free of charge.”⁸⁹

CDC-PEP was publicly disseminated before February 3, 2005. A CDC website archive of past issues of MMWR-RR lists the date of publication of Vol. 54(RR-2) as January 21, 2005.⁹⁰ The Internet Archives also captured the MMWR webpage announcing the availability of CDC-PEP on January 21, 2005.⁹¹ CDC-PEP also was available in libraries at least as early as January 28, 2005.⁹² MMWR-RR publication staff also represented to Petitioner’s counsel that CDC-PEP was made available on their website as from January 21, 2005,⁹³ and the CDC

⁸⁸ *Id.* back-cover-2; Ex. 1139 (“Wayback-Decl.-II”), 6 (volumes of MMWR-RR from Volume 39, with publications dating from 1990-2003).

⁸⁹ CDC-PEP, back-cover-2.

⁹⁰ Ex. 1124 (“CDC-Archive”), 3.

⁹¹ Wayback-Decl.-II, 8.

⁹² Ex. 1128 (“UCSD-Decl.”) ¶8.

⁹³ Ex. 1140 (“Kushan-Decl.”) ¶¶6-11.

webpage announcing CDC-PEP indicates the webpage was last reviewed and converted on January 11, 2005 (below), which matches the metadata of the CDC-PEP file sent to Petitioner’s counsel by MMWR-RR publication staff.⁹⁴

Page converted: 1/11/2005



This page last reviewed 1/11/2005

B. Cal-PrEP and CDC-PEP Provide Enabling Descriptions

To anticipate, a prior art reference must provide an enabling disclosure.

Well-settled law holds that a prior art reference provides an enabling disclosure of a therapeutic method if it describes administering the same agent(s) in the claim,

⁹⁴ Ex. 1125 (“CDC-2005 web”), 25; Kushan-Decl. ¶¶8-10.

even without proof that doing so provided the specified therapeutic effect⁹⁵ and even if the method was not ever performed.⁹⁶

Here, Cal-PrEP and CDC-PEP each describe a method of prophylactically administering antiretroviral drugs including Truvada to individuals who are not infected with HIV in order to prevent establishment of HIV infections in those individuals. Cal-PrEP and CDC-PEP thus each teach administering the same two agents—TDF with FTC—in their same, FDA-approved amounts (200 mg FTC and 300 mg TDF) to individuals confirmed to be HIV-negative to prevent HIV infections. Following the methods described in Cal-PrEP and CDC-PEP thus necessarily yields the same result specified in the claims of the '191 Patent, as the

⁹⁵ *Bristol-Myers*, 246 F.3d at 1378 (prior art showing performance of a claimed method need not report desired therapeutic result); *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) (prior art need not report results inherent to process); *In re Gleave*, 560 F.3d 1331, 1335-36 (Fed. Cir. 2009) (“a prior art reference need not disclose ‘proof of efficacy’ to anticipate the claim.”) (citation omitted).

⁹⁶ *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003) (prior art anticipates if it provides enabling description of process).

same two operative steps in these various claims are described in these references. Each of Cal-PrEP and CDC-PEP also provides extensive details about their methods along with citations to literature to support performing them, and thereby provides fully enabling disclosures of those methods.

C. Claims 1-19 Are Anticipated by Cal-PrEP

1. Overview of Cal-PrEP

Cal-PrEP describes a method of prophylactically administering antiretroviral drugs to “high-risk” individuals who are not infected with HIV before they have an actual or potential exposure to HIV to prevent infection:

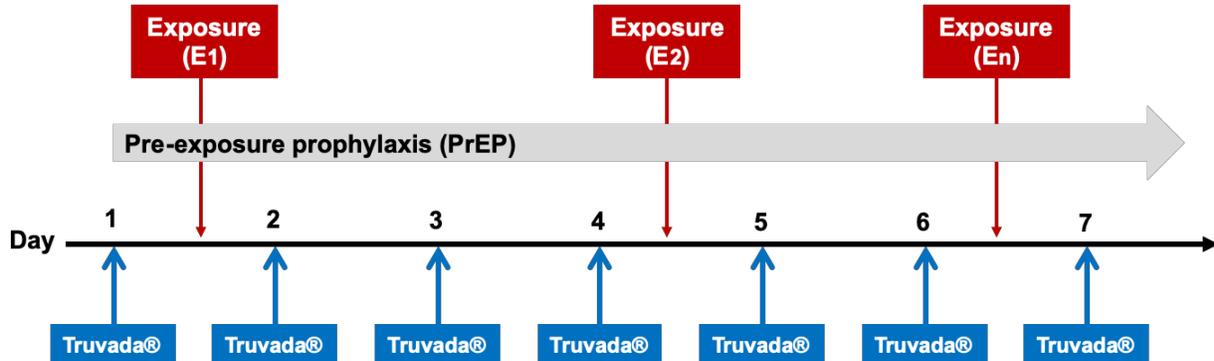
Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection. PrEP should be distinguished from postexposure prophylaxis (PEP), in which an individual takes ARVs soon after a potential HIV exposure with the goal of reducing the likelihood of infection.⁹⁷

Cal-PrEP indicates that TDF is the most suitable NRTI to use in PrEP, and identifies Truvada as one of two TDF-based drug products to use in PrEP.⁹⁸

⁹⁷ Cal-PrEP, 1, 3 (same).

⁹⁸ *Id.* 11.

Cal-PrEP's regimen when followed by a high-risk individual who has multiple HIV exposures (E_1, E_2, \dots, E_n) is illustrated below:⁹⁹



Cal-PrEP explains that its regimen was based on prior experiences with chemoprophylaxis.¹⁰⁰ It summarizes prophylactic use of antiretrovirals to prevent HIV infections following exposures in occupational (e.g., healthcare worker) as well as non-occupational (e.g., sexual and drug use) settings,¹⁰¹ and discusses experiences using antiretrovirals to prevent transmission of HIV from an infected mother to her uninfected child through birth or breastfeeding, observing the latter

⁹⁹ Youle-Decl. ¶¶164-65.

¹⁰⁰ Cal-PrEP, 4.

¹⁰¹ *Id.* 4, 8-11.

“has been shown to dramatically reduce the odds for perinatal HIV transmission.”¹⁰²

Cal-PrEP also describes initiated or planned clinical trials for evaluating PrEP regimens in different cohorts of at-risk individuals.¹⁰³ It observes that, from an epidemiological perspective, whether PrEP will be a success (i.e., whether it reduces rates of infection in a community) depends on several factors, including the risk-taking nature of individuals,¹⁰⁴ whether PrEP alters risk-taking,¹⁰⁵ whether PrEP is supported by healthcare providers and communities,¹⁰⁶ and potential barriers to access to antiretrovirals.¹⁰⁷

Importantly, a skilled person would not have understood these epidemiological questions about whether PrEP will reduce rates of infection in a

¹⁰² *Id.* 5.

¹⁰³ *Id.* 6-11.

¹⁰⁴ *Id.* 19-20.

¹⁰⁵ *Id.* 20-21.

¹⁰⁶ *Id.* 22-23.

¹⁰⁷ *Id.* 24-26.

community as casting doubt that a PrEP regimen based on Truvada (TDF+FTC) would be effective in any individual who followed it properly.¹⁰⁸

2. Independent Claims 1 and 13

Cal-PrEP anticipates Claims 1 and 13 of the '191 Patent because it describes selecting an HIV-uninfected (HIV-seronegative) individual and administering to that individual pharmaceutically effective amounts of TDF+FTC in the form of Truvada prior to an exposure.

a. Preambles

Cal-PrEP describes administering antiretroviral drugs to HIV-uninfected individuals before they are exposed to HIV in order to prevent an infection: “Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection.”¹⁰⁹ While the preambles of Claims 1 and 13 are not limiting, Cal-PrEP nonetheless describes a process that meets each.

¹⁰⁸ Youle-Decl. ¶¶150, 252; Cal-PrEP, 4; Tsai-1998, 4265.

¹⁰⁹ Cal-PrEP, 1 (emphasis added); Youle-Decl. ¶¶165-67.

- b. “[S]electing” “a primate host not infected with the immunodeficiency retrovirus” [1] / “an uninfected human that does not have the self-replicating infection” [13]

Cal-PrEP teaches administering antiretroviral agents to HIV-uninfected individuals (“*primate host*”/“*human*”).¹¹⁰ It indicates that potential candidates are to be screened for eligibility for PrEP, and must be confirmed to be HIV-negative before beginning PrEP (“Planned studies of PrEP will screen for HIV infection prior to enrollment.”).¹¹¹ Cal-PrEP also indicates that being HIV-positive is a basis for excluding individuals from PrEP clinical trials conducted in the 2004/2005-time frame.¹¹² Cal-PrEP thus teaches the “selecting” step of Claims 1 and 13.

- c. “[A]dministering...a combination comprising: (i) a pharmaceutically effective amount of emtricitabine and (ii) a pharmaceutically effective amount of tenofovir or [TDF]” “prior to the exposure” [1] / “prior to a potential

¹¹⁰ Cal-PrEP, 3; Youle-Decl. ¶¶165, 168.

¹¹¹ Cal-PrEP, 13.

¹¹² *Id.* (“Planned studies of PrEP will screen for HIV infection prior to enrollment....”). A “seronegative” individual is HIV-negative based on a serum antibody test. *Id.* 11; Youle-Decl. ¶166.

exposure” [13] “wherein the combination is administered orally in tablet form” [1] / “in a tablet” [13]

Cal-PrEP describes administering antiretroviral agents to HIV-uninfected individuals prior to an actual or potential exposure to HIV in order to prevent an HIV infection. As it states:

PrEP involves the use of antiretroviral drugs (ARVs) by an individual prior to potential HIV exposure, in order to reduce the likelihood of HIV infection.¹¹³

Cal-PrEP identifies the properties of antiretroviral agents that make them well-suited for use in PrEP, stating:

To be ideal for use as PrEP, a drug should be potent, able to be dosed once daily, have a favorable toxicity profile, and not promote development of high-level viral resistance based on a single mutation. In addition, drugs whose mechanisms of action focus on pre-integration phases of the viral life cycle (prior to completion of effective viral

¹¹³ Cal-PrEP, 3 (emphasis added); *see also id.* 1 (“Pre-exposure prophylaxis (PrEP) is a novel approach to HIV prevention in which antiretroviral drugs (ARVs) are used by an individual prior to potential HIV exposure to reduce the likelihood of infection.”).

integration into host cell DNA) are, at least in theory, likely to be more effective than those that focus on post-integration.¹¹⁴

Cal-PrEP then explains that FTC and TDF have these features. Regarding FTC, it explains:

Of the NRTIs, several drugs have characteristics that may limit their potential as PrEP candidates. Lamivudine (3TC) and emtricitabine (FTC) cause few toxicities and may be taken once daily, but both are susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone.¹¹⁵

Cal-PrEP's observation that FTC monotherapy can lead to resistance would have been understood by the skilled person as indicating FTC should be co-administered with another antiretroviral.¹¹⁶

Cal-PrEP then states that TDF is the “most suitable” NRTI for use in PrEP regimens, explaining that it provides the best combination of features for use in PrEP regimens and stating, *inter alia*, that it is “a relatively safe agent with few

¹¹⁴ *Id.* 11.

¹¹⁵ *Id.* (emphasis added).

¹¹⁶ Youle-Decl. ¶¶163, 227; Saag, 29.

adverse side-effects and interactions with other drugs.”¹¹⁷ Cal-PrEP specifically identifies Truvada as one of two TDF-based drug products that can be used in PrEP, stating:

Tenofovir disoproxil fumarate (TDF) is the NRTI that is currently most suitable for use as PrEP. TDF is potent, can be dosed once daily, and has a relatively favorable toxicity profile.... TDF was approved by FDA in 2001 to treat HIV infection and is formulated as a once-daily, 300 mg oral tablet (Viread[®]); a once-daily, fixed-dose combination tablet of TDF and emtricitabine (Truvada[™]) was approved in August 2004 (both Gilead Sciences, Inc., Foster City, CA).¹¹⁸

Cal-PrEP also recommends use of FDA-approved antiretroviral products,¹¹⁹ which a skilled person would understand to mean that such drugs should be used in their FDA-approved doses.¹²⁰ Truvada contains FDA-approved doses of 200 mg FTC and 300 mg TDF,¹²¹ the same doses in the FDA-approved single-agent

¹¹⁷ Cal-PrEP, 11-12.

¹¹⁸ *Id.* 11 (emphasis added).

¹¹⁹ *Id.* 10-11.

¹²⁰ Youle-Decl. ¶237.

¹²¹ Truvada[®]-Label, 21; Youle-Decl. ¶92.

formulations of TDF (Viread) and FTC (Emtriva). When Truvada is administered to a human, it will suppress HIV viral replication and exhibit potent antiviral activity against HIV.¹²² By doing so, Truvada (as well as each of its constituent agents) not only effectively treats an HIV infection but prevents establishment of an HIV infection.¹²³

The '191 Patent does not identify what amounts of TDF and FTC constitute a “pharmaceutically effective amount” of either agent, stating instead that doses should be selected to “create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure.”¹²⁴ Clinical evidence demonstrates that occurs when Truvada, with its FDA-approved doses of 300 mg of TDF and 200 mg of FTC, is administered.¹²⁵ The '191 Patent also observes that “[p]referably, NRTI and NtRTI prophylactic dosing according to the present invention uses as a starting point the maximal

¹²² See *supra* §IV.D; CDC-PEP, 8; Truvada®-Label, 2-3; Youle-Decl. ¶95.

¹²³ See Youle-Decl. ¶¶92, 237, 242; Dumond-PRN, 14-15.

¹²⁴ '191 Patent, 6:29-32.

¹²⁵ Truvada®-Label, 1; Viread®-Label, i; Emtriva®-Label, 5.

recommended tolerated dosing levels for the given active agent combination associated with HAART treatment protocols.”¹²⁶

Cal-PrEP also teaches *orally* administering TDF+FTC *in a tablet*, given that Truvada is a tablet designed for oral ingestion.¹²⁷

Cal-PrEP thus teaches orally administering Truvada in a tablet to an uninfected individual before an HIV exposure, which results in that individual being given pharmaceutically effective amounts of TDF and FTC as Claims 1 and 13 specify.

d. “Thereby” Clauses

While the “thereby” clauses of Claims 1 and 13 are not limiting (*see* §V.C.2.a), Cal-PrEP necessarily satisfies each. Cal-PrEP teaches administering Truvada to an HIV-uninfected individual before an HIV exposure, which results in oral administration to that individual of the same “pharmaceutically effective” amounts of TDF and FTC that the claims and ’191 Patent disclosure say will protect the host from an HIV infection or will inhibit establishment of infection.

¹²⁶ ’191 Patent, 6:44-49.

¹²⁷ Cal-PrEP, 11; Truvada®-Label, 1 (“TRUVADA Tablets are for oral administration.”).

Consequently, administering Truvada as Cal-PrEP teaches will both “*protect*” the individual from an HIV infection (“*a self-replicating infection...*”) and will “*inhibit establishment*” of an HIV infection as Claims 1 and 13 specify.

As Cal-PrEP describes every element of Claims 1 and 13, it anticipates both claims.

3. Claims 2-3

Claim 2 specifies the primate host is an “*adult human,*” while Claim 3 specifies the adult human is a “*male.*” Cal-PrEP indicates that candidates for prophylaxis include, *inter alia*, men who have sex with men (“MSM”), i.e., adult human males.¹²⁸

4. Claims 4, 14, and 17

Claims 4, 14, and 17 specify, respectively, that TDF+FTC are “*in a combined single tablet,*” “*compounded into a single tablet,*” or “*formulated in a single tablet.*” Truvada is a single tablet that results from compounding of TDF+FTC into a single formulation for oral administration to humans.¹²⁹ Cal-

¹²⁸ Cal-PrEP, 4, 7, Table 1.

¹²⁹ Truvada®-Label, 1; Youle-Decl. ¶92.

PrEP thus teaches administration of a single tablet comprised of TDF+FTC as Claims 4, 14, and 17 specify.¹³⁰

5. Claim 5

Claim 5 requires the “*immunodeficiency retrovirus*” to be a “*human immunodeficiency virus*.” Cal-PrEP proposes the use of PrEP for HIV.¹³¹

6. Claim 6

Claim 6 specifies the “*humans [sic] immunodeficiency virus (HIV) is HIV-1.*” The most prevalent strain of HIV in the U.S. in 2005 and today is HIV-1, with 99.9% of cases involving HIV-1.¹³² Cal-PrEP focuses on Californians, and thus would be understood as teaching use of chemoprophylaxis of HIV-1 infections.¹³³

7. Claims 7 and 16

Claim 7 specifies a “*rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus,*” while Claim 16 specifies the exposure

¹³⁰ Cal-PrEP, 11.

¹³¹ *Id.* 1.

¹³² Ex. 1056 (“Torian”), 1334; Ex. 1057 (“CDC-Surveillance”), 986.

¹³³ Cal-PrEP, 2, 7 (Table 1); *see* Youle-Decl. ¶¶91, 141.

“comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.”

Cal-PrEP explains that PrEP is “targeted to MSM, [and] female partners of MSM...”¹³⁴ It also describes use of PrEP in “high-risk, HIV-negative MSM” and “[f]emale commercial sex workers.”¹³⁵ Men within the MSM category are exposed to HIV rectally, orally, and through the reproductive organs, while women who are partners of MSM and female sex workers are exposed to HIV vaginally, orally, and rectally.¹³⁶ Thus, Cal-PrEP teaches use of HIV chemoprophylaxis to prevent HIV infection in one or more of the manners of exposure in Claims 7 and 16.

8. Claims 8, 12, and 18

Claim 8 specifies “*administering 200 milligrams (mg) of emtricitabine to the primate host.*” Claims 12 and 18 specify “*wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disoproxil fumarate.*” Cal-

¹³⁴ Cal-PrEP, 1.

¹³⁵ *Id.* 8-9; *see also id.* 7 (Table 1).

¹³⁶ *See Youle-Decl.* ¶143.

PrEP teaches use of Truvada in PrEP, which results in administration of 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate to the individual.¹³⁷

9. Claim 9

Claim 9 specifies that TDF+FTC is to be “*administered daily for several days, weeks or months.*” Because the claim is written with the disjunctive “or,” it encompasses administrations that last as few as “*several days.*”¹³⁸

Cal-PrEP describes PrEP regimens being tested in clinical studies in which TDF is administered to subjects for a period of 9 to 24 months.¹³⁹ A skilled person would understand from Cal-PrEP’s description of these clinical trials that study participants will take the TDF drug (e.g., Truvada) daily for the specified period

¹³⁷ Truvada®-Label, 21.

¹³⁸ *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1199 (Fed. Cir. 2013).

¹³⁹ Cal-PrEP, 8-9, 12 (“The PrEP studies described in Section II are providing participants with 300 mg TDF tablets (or placebo) to be taken once daily during the study period.”); Youle-Decl. ¶203.

(e.g., 9, 12 or 24 months).¹⁴⁰ Cal-PrEP also explains that “individuals take PrEP throughout their sexual lifetimes.”¹⁴¹

Cal-PrEP also indicates that FDA-approved antiretroviral products are to be used, and identifies two such products: Viread (TDF) and Truvada (TDF+FTC).¹⁴² A skilled person would understand from Cal-PrEP that these products should be used in their FDA-approved forms.¹⁴³

Cal-PrEP thus anticipates Claim 9.

10. Claims 10 and 19

Claims 10 and 19 specify the combination is “*administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus,*” and, like Claim 9, encompass administrations that last “*several days*” before and after an exposure.

¹⁴⁰ Youle-Decl. ¶203.

¹⁴¹ Cal-PrEP 22; Youle-Decl. ¶145.

¹⁴² Cal-PrEP, 11.

¹⁴³ *Id.*; Truvada®-Label, 20; Youle-Decl. ¶¶159, 201.

Cal-PrEP describes clinical trials in which antiretroviral agents are administered for extended periods (i.e., 9 to 24 months) to high-risk individuals.¹⁴⁴ Cal-PrEP justifies its PrEP regimen by reasoning that high-risk individuals are likely to engage in conduct that repeatedly exposes them to HIV during any particular period of time, and that if such individuals are on PrEP when those exposures occur, that will decrease the likelihood of infection.¹⁴⁵ When HIV exposures might occur after any individual's commencement of PrEP, and how frequently they may occur while that individual is on PrEP, will depend on that individual's conduct. Consistent with this, Cal-PrEP instructs that while patients are on the PrEP regimen, they are to be continuously counseled on ways to decrease high-risk activity, are to be repeatedly tested for HIV infection,¹⁴⁶ and are not to suspend taking antiretrovirals after an initial exposure.¹⁴⁷

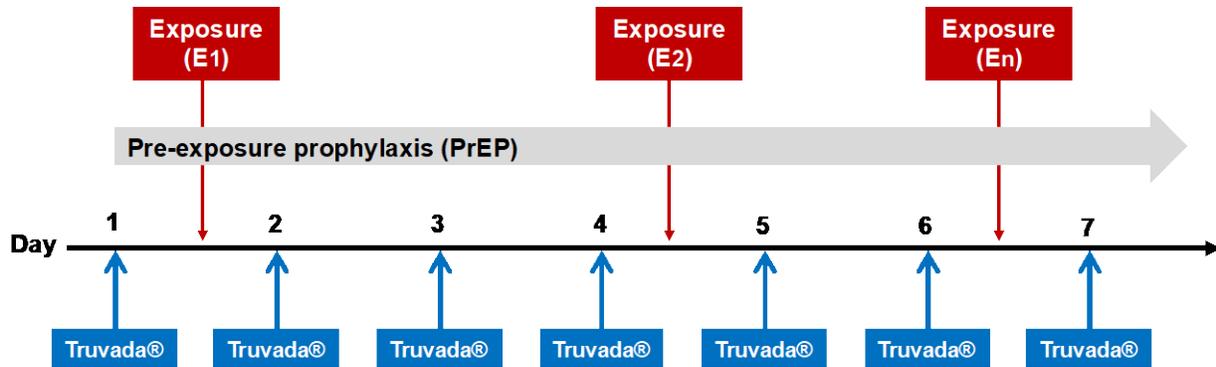
¹⁴⁴ Cal-PrEP, 8-9, 12.

¹⁴⁵ *Id.* 6-10; Youle-Decl. ¶149.

¹⁴⁶ Cal-PrEP, 9, 13-14; Youle-Decl. ¶260.

¹⁴⁷ Cal-PrEP, 8-9, 12 (“[T]ablets (or placebo) [are] to be taken once daily during the study period.”) (emphasis added); Youle-Decl. ¶¶149, 201, 203.

Cal-PrEP thus describes a regimen in which, relative to any of the daily administrations of antiretrovirals, some HIV exposures will occur in a high-risk individual several days before and several days after that HIV exposure (as illustrated below).¹⁴⁸



Cal-PrEP also cites Tsai-1995, a study in which antiretrovirals were administered for multiple days, both before and after exposure to the virus.¹⁴⁹

Cal-PrEP thus teaches administration of Truvada (TDF+FTC) to high-risk individuals that will occur several days before and several days after any individual HIV exposures, as Claims 10 and 19 specify.

¹⁴⁸ Youle-Decl. ¶164.

¹⁴⁹ Tsai-1995, 1197.

11. Claims 11 and 15

Claims 11 and 15 each specify that the administration of TDF+FTC results in “*an absence of persistent viremia and seroconversion.*”

The PrEP regimen described in Cal-PrEP is designed to prevent HIV infection after exposure in an uninfected human subject.¹⁵⁰ Before February 2005, physicians considered the absence of viremia and seroconversion to demonstrate an absence of HIV infection.¹⁵¹ Viremia was conventionally determined by evaluating the presence or absence of HIV in the patient (i.e., “viral load”), while seroconversion was determined by detection of a minimum quantity of anti-HIV antibodies in the patient’s blood.¹⁵²

Cal-PrEP teaches testing for viremia and seroconversion to determine if a subject has become infected with HIV under PrEP. For example, it points to the absence of viremia and seroconversion in animals exposed to SIV as evidence that PrEP was effective to prevent infection.¹⁵³ A skilled person would understand

¹⁵⁰ See *supra* §VI.C.1.

¹⁵¹ Youle-Decl. ¶¶183, 166-67.

¹⁵² *Id.*; see also Ex. 1110 (“Fearon”), 26-29.

¹⁵³ Cal-PrEP, 8, n.32-33 (citing Tsai-1995, Van-Rompay-1998).

from Cal-PrEP that negative test results for persistent viremia and seroconversion indicates successful prophylaxis.¹⁵⁴

D. Claims 1 to 19 Would Have Been Obvious

Patent Owner may contend that Cal-PrEP does not describe the method of Claims 1 to 19, pointing to Cal-PrEP's observation that clinical trials to test its effectiveness were underway but not completed. But Cal-PrEP describes administering the same agents to the same subjects in the same doses for the same purpose as the contested claims, and thus necessarily describes the same process.¹⁵⁵

Regardless, a skilled person would have found Cal-PrEP to provide a specific motivation (i.e., the need to decrease rates of HIV infections in high-risk individuals and within their communities) to modify the PEP regimen described in CDC-PEP by administering Truvada (TDF+FTC) to high-risk individuals before (rather than after) an actual HIV exposure. A skilled person thus would have found it obvious to administer Truvada to an uninfected individual before an HIV exposure to prevent an HIV infection and would have reasonably expected doing so to be effective based on, *inter alia*, experiences with PEP. Consequently, each

¹⁵⁴ Youle-Decl. ¶¶166-67.

¹⁵⁵ See, e.g., *Bristol-Myers*, 246 F.3d at 1378; *Rasmussen*, 413 F.3d at 1326.

of the claimed methods would have been obvious based on CDC-PEP in view of Cal-PrEP in February 2005.

1. Overview of CDC-PEP

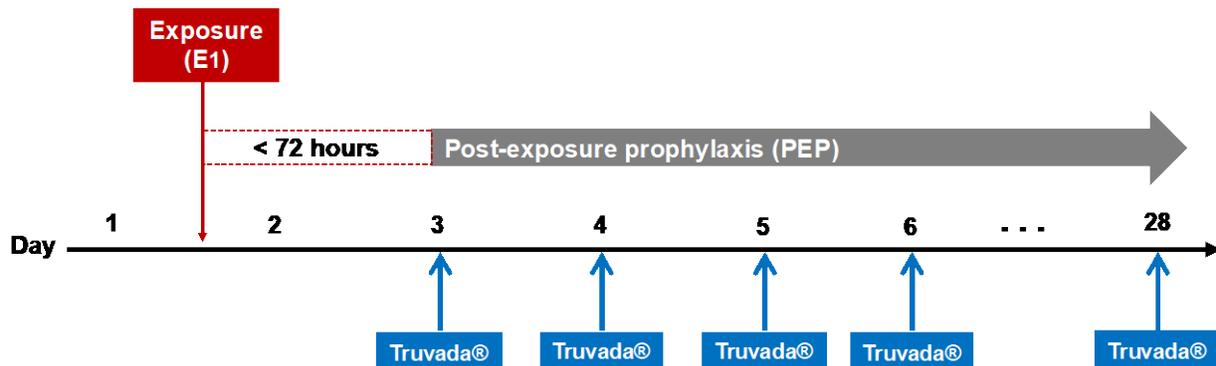
CDC-PEP describes a regimen of daily administrations of combinations of antiretroviral agents for an extended period following an HIV exposure (i.e., post-exposure prophylaxis or PEP) to prevent an HIV infection:

A 28-day course of HAART¹⁵⁶ is recommended for persons who have had nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a person[] known to be HIV infected.¹⁵⁷

¹⁵⁶ Highly active antiretroviral therapy (HAART) involves daily administrations of two or more antiretroviral agents. *See* CDC-PEP, 8; '191 Patent, 5:20-29.

¹⁵⁷ CDC-PEP, 8.

PEP is illustrated below:¹⁵⁸



CDC-PEP identifies TDF+FTC as one of two “preferred” backbone combinations to use in PEP, and notes that Truvada is an oral formulation containing 300 mg of TDF and 200 mg of FTC.¹⁵⁹ CDC-PEP notes “no evidence indicates that any specific antiretroviral medication...is optimal,” but indicates certain regimens are “preferred.”¹⁶⁰ CDC-PEP then recommends two “NNRTI-based” backbone regimens: efavirenz plus either (i) lamivudine plus zidovudine or (ii) emtricitabine plus tenofovir.¹⁶¹

¹⁵⁸ Youle-Decl. ¶174.

¹⁵⁹ CDC-PEP, 9-10.

¹⁶⁰ *Id.* 8.

¹⁶¹ *Id.* 9, Table 2.

TABLE 2. Antiretroviral regimens for nonoccupational postexposure prophylaxis of HIV infection

Preferred regimens	
NNRTI*-based	Efavirenz [†] plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)
Protease inhibitor (PI)-based	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus zidovudine

The word “plus” after efavirenz (an NNRTI) in Table 2 indicates this agent is to be combined with one of the two backbone regimens: either two NRTIs (lamivudine plus zidovudine) or one NRTI (emtricitabine) and one NtRTI (tenofovir).¹⁶²

Table 3 of CDC-PEP indicates that both backbones can be provided through administration of a single combination formulation, either: (i) “Combivir®” for the lamivudine plus zidovudine backbone or (ii) Truvada for emtricitabine plus tenofovir (in the form of TDF) backbone. CDC-PEP labels Truvada (TDF+FTC) one of two “preferred regimens for prophylaxis,¹⁶³ specifying use of “1 tablet once daily 200 mg emtricitabine/300 mg tenofovir” in the form of Truvada.¹⁶⁴

¹⁶² Youle-Decl., ¶176.

¹⁶³ CDC-PEP, 9, Table 2.

¹⁶⁴ *Id.* 10, Table 3; Youle-Decl. ¶¶171, 176.

TABLE 3. Highly active antiretroviral therapy medications, adult dosage, cost, and side effects

Medication	Adult dosage*	Cost (in dollars) for 4 weeks*	Side effects and toxicities
Combination tablets			
Lopinavir/ritonavir (Kaletra [®]) §	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	650	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; and pancreatitis
→ Zidovudine/lamivudine (Combivir [®])	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	640	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir [®])	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/ 300 mg abacavir	1,020	See following individual medications
Lamivudine/abacavir (Epzicom [®])	1 tablet once daily 300 mg lamivudine/600 mg abacavir	760	See following individual medications
→ Emtricitabine/tenofovir (Truvada [®])	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	800	See following individual medications

While CDC-PEP proposes use of a third ARV, it elsewhere explains that “[n]o evidence indicates that a three-drug HAART regimen is more likely to be effective than a two-drug regimen” in prophylaxis.¹⁶⁵ CDC-PEP also recommends use of just two agents—one NRTI and one NtRTI—in situations where the clinician or patient has concerns over the individual taking three antiretroviral agents.¹⁶⁶

CDC-PEP indicates the PEP strategy is based on “[e]vidence from animal studies and human observational studies [which] demonstrate that [PEP] administered within 48-72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational

¹⁶⁵ CDC-PEP, 8. The claims of the ’191 Patent encompass administration of a third agent in addition to TDF and FTC by use of “comprising” language.

¹⁶⁶ *Id.*; Youle-Decl. ¶177.

exposures.”¹⁶⁷ CDC-PEP also identifies non-clinical and clinical evidence supporting the efficacy of PEP in HIV prophylaxis:

[D]ata are available from animal transmission models, perinatal clinical trials, studies of health-care workers receiving prophylaxis after occupational exposures, and from observational studies.¹⁶⁸

For example, the CDC notes that providing ARVs in a health-worker prophylaxis study “was associated with an 81% decrease in the risk for acquiring HIV.”¹⁶⁹

CDC-PEP encourages use of PEP “as soon as possible” after exposure, and no later than 72 hours after exposure, because “[t]he sooner [PEP is administered after exposure, the more likely it is to interrupt transmission.”¹⁷⁰ CDC-PEP also explains PEP is warranted despite side-effects of antiretrovirals, explaining:

¹⁶⁷ CDC-PEP, 8.

¹⁶⁸ *Id.* 2.

¹⁶⁹ *Id.* 3.

¹⁷⁰ *Id.* 8 (“A 28-day course of HAART is recommended for persons who have had nonoccupational exposure...when the person seeks care within 72 hours of exposure.”); *see also id.* 9, 15 (“Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon

Because HIV is an incurable transmissible infection that affects the quality and duration of life, HAART should be used to maximally suppress local viral replication that otherwise might occur in the days after exposure and potentially lead to a disseminated, established infection.¹⁷¹

CDC-PEP likewise observes that “[i]nitial concerns about severe side effects and toxicities have been ameliorated by experience with health-care workers who have taken PEP after occupational exposures.”¹⁷²

The use of combinations of antiretrovirals also was known to mitigate the risk of viral resistance.¹⁷³ In addition, physicians prefer backbones based on a single pill because they facilitate compliance, which is critically important in preventing HIV.¹⁷⁴

as possible within 48-72 hours... and continued for 28 days might reduce the likelihood of transmission.”).

¹⁷¹ *Id.* 8.

¹⁷² *Id.* 4.

¹⁷³ *Id.* 5; Youle-Decl. ¶¶222, 224, 116; Gerberding, 828.

¹⁷⁴ Youle-Decl. ¶103.

2. A Skilled Person Would Have Been Motivated to Commence Prophylaxis Before an Exposure Based on Cal-PrEP

By February 2005, a skilled person would have known from CDC-PEP and their own experiences using the PEP regimen that starting administration of TDF+FTC within 72 hours after an HIV exposure can prevent establishment of an HIV infection.¹⁷⁵ As CDC-PEP teaches, commencing ARV administration as soon as possible after the HIV exposure is a key factor influencing success of that regimen.¹⁷⁶ Indeed, CDC-PEP emphasizes that “[t]he sooner [PEP] is administered after exposure, the more likely it is to interrupt transmission.”¹⁷⁷

The skilled person also would have known that antiretrovirals “interrupt transmission” of HIV by actively suppressing HIV viral replication at the initial site of HIV exposure in the body.¹⁷⁸ That person likewise knew that antiretrovirals

¹⁷⁵ CDC-PEP at 8-12; Youle-Decl. ¶¶175, 179.

¹⁷⁶ CDC-PEP, 8.

¹⁷⁷ *Id.* 8, 15 (“Accumulated data from animal and human clinical and observational studies demonstrate that antiretroviral therapy initiated as soon as possible within 48-72 hours....”); Youle-Decl. ¶¶246, 129-30; CDC-2001, 26.

¹⁷⁸ CDC-PEP, 8; Youle-Decl. ¶¶247-48.

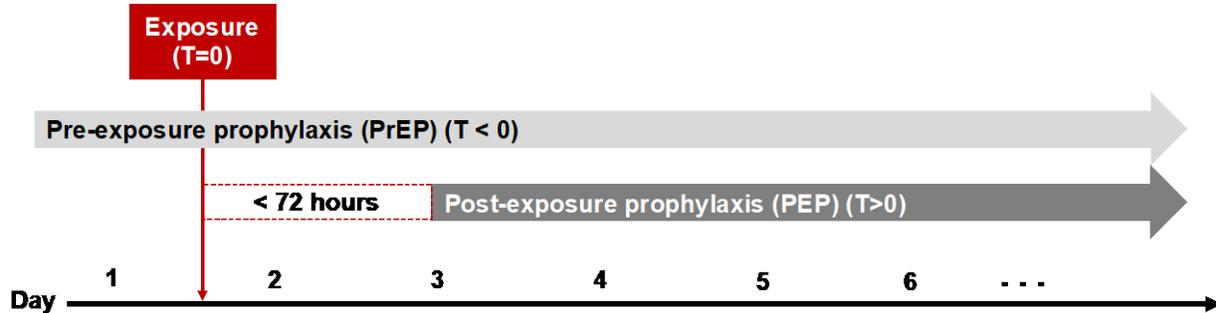
require time after ingestion to transit to the sites of an HIV exposure (e.g., the mucosa) and create drug concentrations at those sites sufficient to suppress HIV replication—at least two hours for TDF and FTC.¹⁷⁹ The skilled person thus would have recognized that the theoretically optimal time to administer TDF+FTC to prevent HIV infection under the PEP regimen would be several hours before an HIV exposure. Doing that would create the maximally suppressive effect of antiretrovirals at the site of the exposure starting at the exact moment of the HIV exposure, and, if maintained without interruption, would maximally inhibit HIV replication within the founder cell population.¹⁸⁰ The skilled person, thus, would have been motivated to administer antiretrovirals even before an HIV exposure to maximize the effectiveness of antiretroviral prophylaxis.

The skilled person further would have recognized that the PrEP regimen in Cal-PrEP differs from the PEP regimen described in CDC-PEP solely with respect to timing: the PrEP regimen effectively shifts the start of a PEP regimen from a

¹⁷⁹ Ex. 1079 (“Dumond-PRN”), 15; Youle-Decl. ¶¶244, 131.

¹⁸⁰ Youle-Decl. ¶¶131-33; Saag, 28.

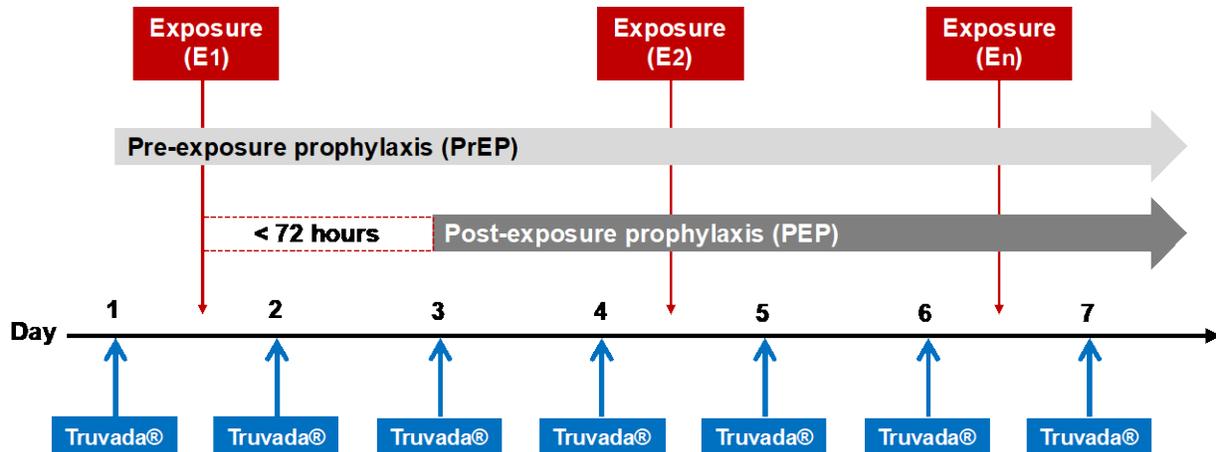
time immediately after ($T > 0$) an HIV exposure to a time prior to that exposure ($T < 0$).¹⁸¹



Indeed, the skilled person would have recognized that a “high risk” individual, such as a sex worker, placed on a 28-day PEP regimen after a first exposure to HIV cannot be meaningfully differentiated from the same individual on a PrEP regimen—in both, the high-risk individual during that 28-day period will have “an exposure” to HIV multiple times (E_2, \dots, E_n), both before and after taking daily doses of the antiretroviral agents, as illustrated below.¹⁸²

¹⁸¹ Youle-Decl. ¶¶245, 134.

¹⁸² *See id.* ¶¶202, 135.



Before 2005, the guidance in Cal-PrEP provided a specific motivation to the skilled person to alter the PEP regimen in CDC-PEP by administering, *inter alia*, Truvada to “high-risk,” HIV-uninfected individuals before an exposure to HIV (rather than after).¹⁸³ As Cal-PrEP explains, high-risk individuals (e.g., commercial sex workers, intravenous drug users, MSM) engage in conduct that repeatedly exposes them to HIV, and such exposures significantly increase the risks of HIV infection to not only those individuals but to others in their community with whom they interact.¹⁸⁴ Cal-PrEP thus proposes to administer combinations of antiretrovirals (including Truvada) to such high-risk individuals for periods that will span when those individuals are likely to have multiple

¹⁸³ *Id.* ¶136.

¹⁸⁴ Cal-PrEP, 3; Youle-Decl. ¶146; Youle-JIAPAC, 104.

exposures to HIV due to their conduct. Certainly, Cal-PrEP recognizes that antiretrovirals can cause side-effects, and that continued use of them presents risks for individuals who take them for extended periods.¹⁸⁵ But the skilled person would have understood that by nonetheless recommending chemoprophylaxis for these high-risk individuals for extended periods (e.g., 9 to 24 months), Cal-PrEP teaches that the individual and community benefits of preventing HIV infections (i.e., a lifelong, incurable disease) outweigh those risks of potential side-effects.¹⁸⁶

Cal-PrEP justifies its regimen as being part of a broader strategy for reducing the rate of HIV infection in communities—it proposes administering antiretrovirals to uninfected high-risk individuals to not only prevent those individuals from contracting HIV, but to prevent those individuals from infecting others in their community. For example, Cal-PrEP advocates antiretroviral prophylaxis as a supplement to “intensive risk-reduction interventions” proposed in CDC-PEP to prevent HIV infections in high-risk uninfected individuals.¹⁸⁷ Cal-PrEP also observes that behavioral interventions alone have not meaningfully

¹⁸⁵ Cal-PrEP, 10-11.

¹⁸⁶ Youle-Decl. ¶146; Cal-PrEP, 6-10.

¹⁸⁷ CDC-PEP, 6; *see* Youle-Decl. ¶¶145, 147.

reduced HIV infection rates in communities with high-risk individuals in them, and observes that effective epidemiological strategies were urgently needed in such communities.¹⁸⁸

Cal-PrEP thus justifies its recommendation to alter the known PEP strategy by administering Truvada to uninfected high-risk individuals to advance its community-focused goal of reducing the spread of HIV via these individuals in communities where they are active.¹⁸⁹ Indeed, whether PrEP could reduce HIV infection rates in communities was one of the objectives of the clinical trials referenced in Cal-PrEP.¹⁹⁰

3. CDC-PEP and Cal-PrEP Both Recommended Truvada for Prophylaxis of HIV-Uninfected Individuals

CDC-PEP and Cal-PrEP each specifically identify Truvada as a “preferred”¹⁹¹ or “optimal”¹⁹² product to use in their respective chemoprophylaxis

¹⁸⁸ CDC-PEP, 3; Cal-PrEP, 3; Youle-Decl. ¶250.

¹⁸⁹ Youle-Decl. ¶¶147, 149, 250.

¹⁹⁰ *Id.* ¶261.

¹⁹¹ CDC-PEP, 8-9, Table 2; 10, Table 3; *see also supra* §VI.D.1.

¹⁹² Cal-PrEP, 11; *see also* §VI.C.2.c.

regimens for HIV-uninfected individuals. By February 2005, a skilled person also would have been motivated to use Truvada given its favorable side-effects profile relative to Combivir and other antiretrovirals,¹⁹³ and to minimize risks of viral resistance that can arise from TDF or FTC monotherapy.¹⁹⁴

For example, Cal-PrEP notes the “possible emergence of resistance due to selection of the K65R mutation” for TDF monotherapy and that FTC is “susceptible to a single-point mutation at codon 184 that confers resistance, especially when taken alone.”¹⁹⁵ Truvada’s clinical trial results showed no instances of viral resistance.¹⁹⁶ The skilled person thus would have understood that monotherapy-linked risks could be minimized by using Truvada, which combines TDF with FTC.¹⁹⁷

¹⁹³ Moyer, 1; Youle-Decl. ¶237.

¹⁹⁴ *See, e.g., Cal-PrEP*, 11 (“To be ideal for use as PrEP, a drug should...not promote development of high-level viral resistance based on a single mutation.”); Youle-Decl. ¶¶87, 163.

¹⁹⁵ Cal-PrEP, 11 (emphasis added).

¹⁹⁶ Moyer, 1.

¹⁹⁷ Youle-Decl. ¶¶163, 222, 224.

Thus, before February 2005, CDC-PEP taught that Truvada was a “preferred” agent to use in the PEP regimen and Cal-PrEP taught that Truvada met every feature of the “ideal” PrEP agent.¹⁹⁸ Consequently, a skilled person would have found it obvious to use Truvada in the PrEP regimen suggested by CDC-PEP and Cal-PrEP.

4. A Skilled Person Would Reasonably Expect PrEP Using Truvada to be Effective in Preventing HIV Infection

During examination of a related patent, Patent Owner represented to the Patent Office that a skilled person in February 2005 would have doubted that a pre-exposure HIV chemoprophylaxis regimen based on TDF+FTC would have been effective in preventing HIV infection.¹⁹⁹ That assertion has no basis in fact. It also ignores that the claims do not require any particular degree of success, given that the preamble and “thereby” clauses of Claims 1 and 13 are non-limiting.²⁰⁰ And

¹⁹⁸ CDC-PEP, 9, Table 2; Cal-PrEP, 11; Youle-Decl. ¶¶241, 96, 161.

¹⁹⁹ Ex. 1002 (“509 File History”), 82, 116-18.

²⁰⁰ *See supra* §V.C.2.a.

the law only requires a reasonable expectation of success, not certainty, a standard more than met by the scientific evidence known before February 2005.²⁰¹

a. Extensive Experiences with PEP Established a Reasonable Expectation of Success

More than 15 years of experience before February 2005 established that combinations of antiretroviral agents can prevent HIV infections in uninfected individuals after they have been exposed to HIV. Indeed, the CDC's own guidelines (CDC-PEP) rest on the principle that aggressively suppressing HIV viral replication by administering combinations of antiretroviral agents shortly after an HIV exposure will prevent establishment of an HIV infection.²⁰²

CDC-PEP identifies timing, not viral inhibition by ARVs, as the most critical factor in successful prophylaxis, explaining that delays in starting administration of ARVs makes the chemoprophylactic regimen less effective.²⁰³ That observation also makes it clear that administering antiviral agents before an

²⁰¹ *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016).

²⁰² CDC-PEP, 2-4; Youle-Decl. ¶¶130-31.

²⁰³ CDC-PEP, 2.

HIV exposure yields the maximum prophylactic effectiveness, as it will create effective concentrations of the antiretroviral agents at the site of exposure the moment an HIV exposure occurs.²⁰⁴ PrEP, in essence, is the most optimal form of the PEP regimen.

CDC-PEP also catalogs the extensive scientific evidence known before 2005 that supports the effectiveness of antiretroviral-based prophylaxis in preventing HIV infection in uninfected individuals. That evidence includes animal studies, experiences with mother-to-child prophylaxis, observational studies of PEP, and case reports.²⁰⁵ CDC-PEP, for example, refers to data showing an 81% reduction in infections in needle-stick settings using antiretroviral therapy with zidovudine.²⁰⁶ CDC's own reliance on this evidence to support its PEP guidelines directly refutes Patent Owner's assertions during examination of a related patent that a skilled person would not have expected administration of Truvada before an HIV exposure to effectively prevent establishment of an HIV infection in an

²⁰⁴ Youle-Decl. ¶133; Saag, 28.

²⁰⁵ CDC-PEP, 2-4.

²⁰⁶ *Id.* 3.

uninfected individual.²⁰⁷ And expectations of success could only increase with the advances of the early 2000s, particularly clinical experiences with TDF+FTC, which showed effective suppression of viral replication with fewer side-effects than Combivir.²⁰⁸

b. PrEP and PEP Regimens Have the Same Pharmacological Mechanism and Cause the Same Result

A skilled person familiar with how antiretroviral agents such as TDF and FTC work in treatment and in post-exposure prophylaxis would have expected the same pharmacological effect to be observed if the agents are administered before an HIV exposure. That is because the same agents when administered to a human subject at the same doses will cause the same effects—they will create a drug concentration at the site of the exposure that maximally suppresses HIV replication.²⁰⁹ The skilled person thus would have recognized that the way Truvada prevents HIV infection in the human body in the PEP regimen is identical

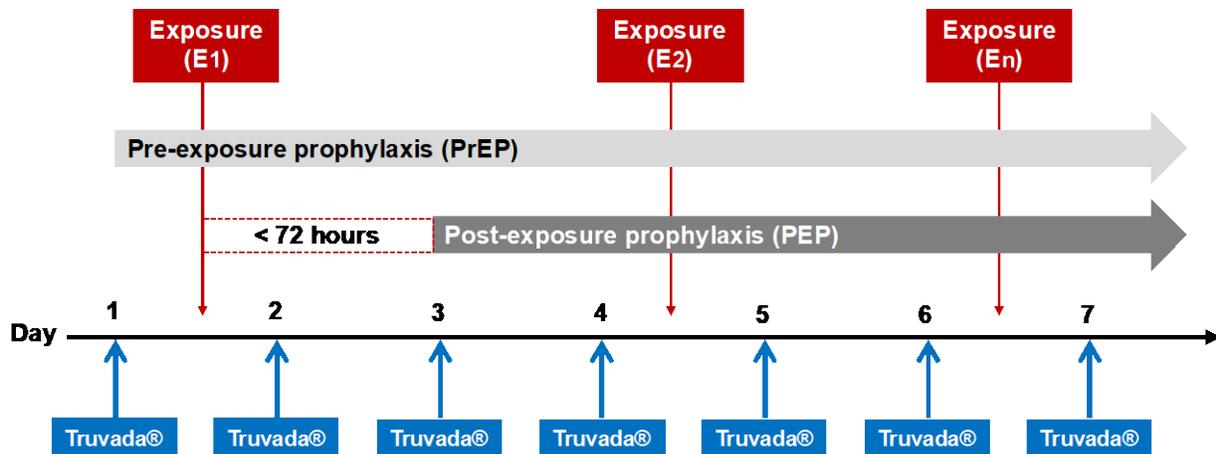
²⁰⁷ See, e.g., '509 File History, 115 (“The art teaches that use of an anti-HIV agent to treat HIV infection does not reasonably predict the ability of that agent to protect against HIV infection.”).

²⁰⁸ Moyer, 1.

²⁰⁹ Youle-Decl. ¶¶242-43, 248.

to the way it does so in a PrEP regimen, and the reasons why PEP is effective in preventing HIV infection are the same reasons it is effective in PrEP.

CDC-PEP and Cal-PrEP also describe performing the same operative steps—orally administering once a day at least 300 mg of TDF and 200 mg of FTC (i.e., Truvada) to an uninfected individual—with the only difference being when those steps are performed. Indeed, a high-risk uninfected individual placed on a Truvada-based PEP regimen who does not become infected and who experiences an additional HIV exposure during the 28-day or longer regimen will meet all the requirements of the contested claims. That is because the HIV-uninfected individual will be given pharmaceutically effective amounts of TDF and FTC before an HIV exposure (i.e., at exposures E₂ or later).²¹⁰



²¹⁰ *Id.* ¶¶135-36.

A skilled person thus would have reasonably expected pre-exposure administration of Truvada to prevent establishment of an HIV infection in an uninfected individual (i.e., PrEP with Truvada), given that post-exposure administration of the same dose of the same two agents (i.e., PEP with Truvada) does.²¹¹

c. Cal-PrEP Described Clinical Trials Focused on Decreasing Community Rates of HIV Infection

Patent Owner may contend that Cal-PrEP's indication that clinical trials were needed to prove the effectiveness of PrEP, coupled with its identification of factors that could limit the effectiveness of PrEP, would have led a skilled person to doubt that Truvada, when administered to an HIV uninfected individual before an HIV exposure, would “protect” a host from a HIV infection or “inhibit establishment” of an infection per Claims 1 and 12. Such contentions have no merit.

Initially, the claims do not require the successful prevention of HIV in every individual—they only require performing the steps of administering pharmaceutically effective amounts of TDF and of FTC to one uninfected

²¹¹ *Id.* ¶¶245, 248.

individual before an HIV exposure. That is precisely what is taught or suggested by both Cal-PrEP and CDC-PEP.

Moreover, nothing in the '191 Patent answers the questions supposedly raised in Cal-PrEP about the feasibility of PrEP. Most notably, the macaque studies reported in the '191 Patent do not address any of the human behavioral factors that Cal-PrEP identifies as potentially limiting the effectiveness of PrEP in slowing the rate of infection. Those factors include, *inter alia*, compliance (i.e., whether patients take the pills each day at the right time), access to drugs, and a variety of societal and behavioral factors.²¹² A skilled person reading Cal-PrEP would have instead recognized that in its ideal implementation (i.e., an individual with a steady supply of Truvada who takes it every day as prescribed), PrEP would be effective in preventing HIV infection in that individual.²¹³

More generally, both Cal-PrEP and CDC-PEP recognize that reducing the rate of HIV infections within a community can be best achieved by a combination of interventions. For example, CDC-PEP instructs caregivers to counsel

²¹² *Id.* ¶¶262, 258.

²¹³ *Id.* ¶¶251-52.

individuals to avoid high-risk activities while on the PEP regimen.²¹⁴ Cal-PrEP likewise explains that to “reduce the occurrence of future HIV exposures,” individuals on PrEP should be continuously counseled on ways to decrease high-risk activity (e.g., abstinence, protective behaviors, and being repeatedly tested for HIV infection).²¹⁵ Cal-PrEP, however, recognized that some patients will not follow advice to reduce high-risk activities, be exposed to HIV, and create risks for the broader community. Cal-PrEP thus portrayed the risk-benefit assessment as tilting in favor of administering antiretroviral agents to HIV-uninfected individuals to span periods of their “high-risk” activities.²¹⁶

Ultimately, the relevant question for obviousness is whether a skilled person would reasonably believe that administering TDF+FTC to one uninfected individual will prevent establishment of an HIV infection in that individual.²¹⁷ More than substantial evidence shows that to be true.

²¹⁴ CDC-PEP, 5.

²¹⁵ Cal-PrEP, 27.

²¹⁶ *Id.* 3.

²¹⁷ Youle-Decl. ¶¶251, 253, 259.

d. HIV Chemoprophylaxis Was Not “Highly Unpredictable”

During examination of a related patent, Patent Owner claimed HIV chemoprophylaxis was “highly unpredictable” for various reasons.²¹⁸ Patent Owner’s assertions are contradicted by the literature and/or are legally irrelevant.

First, Patent Owner cited results from a PrEP trial using a CCR5 inhibitor.²¹⁹ Besides involving an agent with a different mechanism of action than TDF+FTC, those results could not have influenced expectations of a skilled person in February 2005 because they were not published until 2013.²²⁰

Second, Patent Owner portrayed Subbarao-2006 as showing that prophylaxis using TDF monotherapy in animal studies was unsuccessful. But skilled persons—including the CDC and the authors of Subbarao-2006—portrayed these same TDF monotherapy animal studies as being positive clinical results supporting PrEP.²²¹

²¹⁸ ’509 File History, 82, 116-17.

²¹⁹ *Id.* 116; Youle-Decl. ¶¶83, 207.

²²⁰ ’509 File History, 116.

²²¹ Youle-Decl. ¶¶216-19, 233-36.

Notably, Subbarao-2006 reported that even after 14 weekly exposures, “[o]ne macaque (RQ4180) in the daily-TDF group remained uninfected,” and credited that to TDF’s effectiveness, stating “oral TDF must have played a role in preventing infection in this macaque.”²²² Subbarao-2006 also stated “that oral TDF prophylaxis of macaques in our study resulted in a 60% decrease in the per-exposure probability of infection,” thereby providing at least “partial protection” when administered prior to exposure.²²³ And Subbarao-2006 not only reported that “tenofovir prophylaxis may be of benefit” in a pre-exposure setting (noting it delayed median times to infection), but stated this in the paper’s title.²²⁴ Moreover, a commentary published in the same issue of *Science* cited Subbarao-2006’s experimental results as supporting the viability of TDF-based PrEP *combination* therapy, stating “combinations of agents may be more suited for PrEP” than TDF alone, and specifically recommended use of Truvada in PrEP.²²⁵ And other

²²² Ex. 1050 (“Subbarao-2006”), 907, 909; Youle-Decl. ¶217.

²²³ Subbarao-2006, 907; Youle-Decl. ¶216.

²²⁴ *See* Subbarao-2006, 910; *see also id.* 907.

²²⁵ Grant-2006, 875; *see also* Ex. 1053 (“Grant-2005”), 2170; Youle-Decl.

¶¶220-21; *supra* §IV.D.

contemporaneous publications cited other TDF-based PrEP animal studies as supporting the viability of TDF PrEP monotherapy in humans.²²⁶

Post-filing publications from the CDC also directly contradict Patent Owner's assertions. Most notably, in its 2014 PrEP guidelines, the CDC cited Subbarao-2006 as *supporting* the efficacy of TDF in PrEP, stating:

Evidence from these human studies of blood-borne and perinatal transmission as well as studies of vaginal and rectal exposure among animals [FN17-19] *suggested that PrEP (using antiretroviral drugs) could reduce the risk of acquiring HIV infection from sexual and drug-use exposures.*²²⁷

The last assertion made by Patent Owner was that Cambodian TDF PrEP clinical trials were cancelled due to concerns over therapeutic efficacy.²²⁸ That too is incorrect: one report identified concerns over trial participants being unfairly

²²⁶ E.g., Ex. 1051 (“Grant-2006”), 874 (observing that Subbarao’s results “advance[]...the use of antiretroviral drugs in...PrEP...for HIV disease); Ex. 1052 (“Subbarao-2007”), 241 (follow-up publication stating “oral TDF can be initially effective for a while”); Youle-Decl. ¶209.

²²⁷ Ex. 1123 (“CDC-2014”), 14 (emphasis added) (FN17 is Subbarao-2006).

²²⁸ ’509 File History, 114.

exploited as the reason, and that same report observed that tenofovir “has a better safety profile than any anti-HIV drug on the market” and “already has proven to be extremely effective as an HIV preventative in monkey experiments.”²²⁹

And, while Patent Owner asserted during examination of a related patent that “the prior art does not disclose or suggest...selecting a subject not infected with the immunodeficiency retrovirus, and administering a pharmaceutically effective amount of emtricitabine and a pharmaceutically effective amount of tenofovir” for PEP or PrEP,²³⁰ that statement is demonstrably incorrect. As shown in §§VI.B-D, CDC-PEP and Cal-PrEP each are based on the proposition that HIV prophylaxis with Truvada is effective.

E. There Are No Secondary Indicia of Non-Obviousness

Patent Owner may contend that evidence of secondary considerations, such as unexpected results or commercial success, warrant finding the claims non-obvious.²³¹ But to be pertinent to obviousness, the secondary considerations

²²⁹ Ex. 1054 (“Cohen-2004”), 1092.

²³⁰ ’509 File History, 114.

²³¹ Secondary considerations are irrelevant to anticipation.

evidence must have a nexus to *the invention*. “[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.”²³²

Here, the evidence shows that any unexpected results or commercial success of using TDF+FTC in PrEP regimens are attributable to the prior art, not the ’191 Patent. That prior art clearly identifies not only the process of administering Truvada to HIV-uninfected individuals before an HIV exposure to prevent HIV infections but also identifies the characteristics of drugs “ideal for use as PrEP” and explains that “drugs [like NRTIs] whose mechanisms of action focus on pre-integration” are likely to be effective.²³³ Indeed, at best, the ’191 Patent provided simply a confirmation of what scientists knew and expected from the prior art.

Likewise, if “market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.”²³⁴ Gilead holds patents claiming once-daily oral formulations of TDF, FTC, and their combination, which cover all uses of the

²³² *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

²³³ *See, e.g., Cal-PrEP*, 10-11.

²³⁴ *Merck & Co. v. Teva Pharmaceuticals USA*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

compounds.²³⁵ Because market entry for third parties was blocked by Gilead's patents on the Truvada product, any inference of non-obviousness for commercial success of the claimed methods (which concern a use of Truvada) is weak at best.

Other secondary considerations are absent. For example, by February 2005, there was no failure of others or skepticism in the field with respect to Truvada's use in PrEP. Instead, by then, the CDC had recommended its use in both treatment and prophylaxis²³⁶ and skilled persons proposed using it in large-scale PrEP trials.²³⁷ Physicians also had begun recommending Truvada for PrEP to high-risk patients and such individuals began obtaining Truvada from friends to take in prophylaxis before and after high-risk behavior.²³⁸ And Truvada's more recent success in PrEP is not due to anything disclosed in the '191 Patent, but to the efforts of the CDC and Gilead to promote its use.

²³⁵ *E.g.*, U.S. Patent Nos. 5,922,695 (TDF); 6,703,396 (FTC); 8,592,397 (TDF+FTC).

²³⁶ Ex. 1075 ("DHHS-2004"), 14; CDC-PEP, 9 (Table 2).

²³⁷ Youle-Decl. ¶¶230-32; *see also* Ex. 1135 ("Grant-Proposal"), 3-4.

²³⁸ Youle-Decl. ¶241.

Thus, no secondary indicia have a nexus to the claimed methods, and none supports the non-obviousness of the contested claims. Petitioner also submits any evidence of secondary indicia advanced by Patent Owner in its response should be addressed after institution, where that evidence and its relevance can be contested.

VII. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION UNDER 35 U.S.C. §325(D)

Under the relevant factors identified in *Becton Dickinson & Co. v. B. Braun Melsungen AG* and in the Board’s July 2019 Trial Practice Guide Update, the Board should not exercise its discretion under §325(d).²³⁹

This petition proposes different grounds (including anticipation) relative to those at issue during examination of the ’191 Patent, and presents new evidence not considered by the Office—a declaration from Dr. Michael Youle (Ex. 1009), a

²³⁹ Trial Practice Guide, 84 Fed. Reg. 33,925 (July 2019 Update) (“Trial Practice Guide”), 29-30 (factors 1 to 4) (citing *Becton Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017) (precedential)).

noted expert in the field of HIV therapy and prevention.²⁴⁰ This Petition therefore does not present the “same or substantially the same prior art or arguments”²⁴¹ raised or considered during examination of the ’191 Patent or its predecessors (i.e., U.S. Patent Nos. 9,044,509 (“’509 Patent”) and 9,579,333 (“’333 Patent”)).

The examination record of the ’191 Patent also reveals that “the Office erred in evaluating the asserted prior art” during its examination, which further justifies the Board not exercising its discretion here.²⁴² What the ’191 Patent file wrapper shows is that the Examiner rejected claims similar to those in the ’509 Patent as being obvious over seven prior art references, two of which were Cal-PrEP and CDC-PEP.²⁴³ The Examiner correctly observed that Cal-PrEP (also referred to as “Szekeres”) identified (1) the need for biomedical approaches to HIV prevention

²⁴⁰ *Apotex Inc. v. Novartis AG*, IPR2017-00854, Paper 11, 13-14 (P.T.A.B. July 18, 2017).

²⁴¹ 35 U.S.C. §325(d).

²⁴² Trial Practice Guide, 30 (factor 5).

²⁴³ Ex. 1006 (“’191 File History”), 60-61.

including PrEP and that (2) TDF was well-suited for PrEP.²⁴⁴ The Examiner also correctly observed that CDC-PEP disclosed Truvada for use in PEP and that it would have been obvious to treat uninfected individuals who are exposed to or at risk of exposure to HIV with Truvada.²⁴⁵

But rather than address the merits of this rejection, Patent Owner secured an interview with the Examiner, proposed an amendment to add a “tablet” limitation to the ’509 Patent claims, and appeared to convince the Examiner this amended claim would be patentable for the same reasons that the Examiner had found the ’509 Patent claims patentable. As the Examiner’s interview summary states:

Applicants’ attorney indicates that applicants will pursue subject matter within the scope of allowed claim in parent application (now US 9,044,509).... Particularly, claims 1 herein will be amended to the same as claim 1 in ’509, but with a further limitation of the oral dosage form: a tablet. The examiner indicates that such a claim would be allowable for reasons as set forth in the parent application.²⁴⁶

²⁴⁴ *Id.* 60. The Examiner consequently did not observe that Cal-PrEP also identified Truvada as one of two TDF options to use in PrEP.

²⁴⁵ *Id.* 60-61.

²⁴⁶ *Id.* 53 (emphasis added).

Then, when Patent Owner presented this amended “tablet” claim, it stated the Examiner had “confirmed that it was not necessary to address the rejection under 35 U.S.C. §103 if the proposed claim amendments were made in the response.”²⁴⁷

But neither Cal-PrEP nor CDC-PEP was ever cited during examination of the ’509 Patent, much less were the basis of rejections that were imposed and overcome during its examination.²⁴⁸ Thus, the statement in the Examiner’s interview summary form (and reinforced by Patent Owner’s response) that the ’191 Patent claims were patentable *for the same reasons the Examiner had found the ’509 Patent claims patentable* was and is demonstrably false—the ’509 Patent claims were never even considered in connection with Cal-PrEP or CDC-PEP because Patent Owner did not provide those references to the Office until years after the ’509 Patent granted.

The examination record of the ’191 Patent at issue in this petition thus shows that Patent Owner never addressed, much less overcame, any rejection that relied on the substantive teachings of Cal-PrEP and CDC-PEP. What it shows instead is

²⁴⁷ *Id.* 40 (emphasis added).

²⁴⁸ The same Examiner examined all four patents that issued from this family of applications.

that the Examiner mistakenly equated the basis of the rejection of the '191 Patent claims with a rejection imposed over different and much less relevant prior art (i.e., not Cal-PrEP or CDC-PEP) during examination of the '509 Patent claims. The Examiner's mistake improperly equated the significance of teachings in Cal-PrEP and CDC-PEP with those in the references actually used during examination of the '509 Patent, an assumption that is entirely unwarranted. For example, none of the references used during examination of the '509 Patent described use of Truvada in prophylaxis, much less taught the PrEP regimen where TDF and FTC (i.e., Truvada) are administered prior to an HIV exposure.²⁴⁹ As a result, the Office's error evaluating Cal-PrEP and CDC-PEP (i.e., the asserted prior art in this petition) justifies the Board not exercising its discretion under §325(d).

Consequently, because the patentability issues presented in this petition were not considered during examination of the '191 Patent, and because the Examiner erred during the examination of the '191 patent, the Board should not exercise its discretion under §325(d).

²⁴⁹ *E.g.*, '509 File History, 111-15, 490-92.

VIII. CONCLUSION

Petitioner respectfully requests that trial be instituted and that the claims be held unpatentable for the reasons set forth above.

Dated: August 23, 2019

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CERTIFICATE OF COMPLIANCE

I hereby certify that this Petition complies with the type-volume limitations of 37 C.F.R. §42.24, because it contains 12,633 words (as determined by the Microsoft Word word-processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §42.6(e), I hereby certify that on this 23rd day of August, 2019, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by Federal Express on the following counsel:

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Exhibit List

No.	Exhibit Description
1001	U.S. Patent No. 9,044,509 (“509 Patent”)
1002	File History of U.S. Patent No. 9,044,509 (“509 File History”)
1003	U.S. Patent No. 9,579,333 (“333 Patent”)
1004	File History of U.S. Patent No. 9,579,333 (“333 File History”)
1005	U.S. Patent No. 9,937,191 (“191 Patent”)
1006	File History of U.S. Patent No. 9,937,191 (“191 File History”)
1007	U.S. Patent No. 10,335,423 (“423 Patent”)
1008	File History of U.S. Patent No. 10,335,423 (“423 File History”)
1009	Declaration of Michael Youle, MB, ChB (“Youle-Decl.”)
1010	Curriculum Vitae of Michael Youle, MB, ChB
1011	Szekeres et al., “Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians,” Center for HIV Identification, Prevention and Treatment Services (2004) (“Cal-PrEP”)
1012	Centers for Disease Control and Prevention, “Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States,” Recommendations from the U.S. Department of Health and Human Services, Morbidity and Mortality Weekly Report 54(2) (Jan. 21, 2005) (“CDC-PEP”)
1013	Centers for Disease Control and Prevention, “Public Health Service Guidelines for the Management of Health-Care Worker Exposures to HIV and Recommendations for Postexposure Prophylaxis,” Morbidity and Mortality Weekly Report 47(7) (1998) (“CDC-May1998”)
1014	Centers for Disease Control and Prevention, “Report of the NIH Panel to Define Principles of Therapy of HIV Infection and Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and

	Adolescents,” Morbidity and Mortality Weekly Report 47(5) (1998) (“CDC-ARV”)
1015	Hu et al., “Simian Immunodeficiency Virus Rapidly Penetrates the Cervicovaginal Mucosa after Vaginal Inoculation and Infects Intraepithelial Dendritic Cells,” J. Virol. 74(13): 6087–95 (2000) (“Hu”)
1016	De Clercq, “HIV-chemotherapy and -prophylaxis: new drugs, leads and approaches,” Int’l J. Biochem. Cell Bio. 36(9): 1800–22 (2004) (“De Clercq-IJB”)
1017	Bassett et al., “Two Drugs or Three? Balancing Efficacy, Toxicity, and Resistance in Postexposure Prophylaxis for Occupational Exposure to HIV,” Clin. Infect. Dis. 39(3): 395–401 (2004) (“Bassett”)
1018	Coffin, “HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis, and Therapy,” Science 267(5197): 483–9 (1995) (“Coffin”)
1019	Hammer et al., “A Controlled Trial of Two Nucleoside Analogues plus Indinavir in Persons with Human Immunodeficiency Virus Infection and CD4 Cell Counts of 200 per Cubic Millimeter or Less,” N. Engl. J. Med. 337(11): 725–33 (1997) (“Hammer”)
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1021	Barreiro et al., “Combinations of Nucleoside/Nucleotide Analogues for HIV Therapy,” AIDS Rev. 6(4): 234–43 (2004) (“Barreiro”)
1022	Collins, “Tenofovir/FTC Backbone Outperforms AZT/3TC (Combivir) with Efavirenz in Treatment Naive Patients; Reduced Toxicity Drives ITT Viral Efficacy,” HIV i-Base (Jan. 29, 2005), http://i-base.info/htb/7665 (“Collins”)
1023	Gerberding, “Occupational Exposure to HIV in Health Care Settings,” N. Engl. J. Med. 348(9): 826–33 (2003) (“Gerberding”)

1024	Centers for Disease Control and Prevention, “Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis,” <i>Morbidity and Mortality Weekly Report</i> 50(11) (2001) (“CDC-2001”)
1025	Truvada® Label, FDA.gov (Aug. 2004), https://web.archive.org/web/20041014005516/http://www.truvada.com:80/fpi.pdf (“Truvada®-Label”)
1026	Truvada® Approval Letter, FDA.gov (Aug. 2, 2004), http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2004/21752ltr.pdf (“Approval-Letter”)
1027	Viread®-Label, FDA.gov (Oct. 2001), https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21356lbl.pdf (“Viread®-Label”)
1028	Emtriva®-Label, FDA.gov (July 2003), https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21500_emtriva_lbl.pdf (“Emtriva®-Label”)
1029	De Clercq, “Antiviral Drugs in Current Clinical Use,” <i>J. Clin. Virol.</i> 30(2): 115–33 (2004) (“De-Clercq-JCV”)
1030	Bang & Scott, “Emtricitabine: An Antiretroviral Agent for HIV Infection,” <i>Drugs</i> 63(22): 2413–24 (2003) (“Bang”)
1031	Vela et al., “In Vitro Evaluation of the Anti-HIV Activity and Metabolic Interactions of Emtricitabine and Tenofovir,” <i>HIV DART 2004 – Frontiers in Drug Development for Antiretroviral Therapies</i> , Dec. 12-16, 2004, Montego Bay, Jamaica (“Vela”)
1032	Dando & Wagstaff, “Emtricitabine/Tenofovir Disoproxil Fumarate,” <i>Drugs</i> 64(18): 2075–82 (2004) (“Dando”)
1033	Back et al., “The Pharmacology of Antiretroviral Nucleoside and Nucleotide Reverse Transcriptase Inhibitors: Implications for Once-Daily Dosing,” <i>J. Acquir. Immune Defic. Syndr.</i> 39(1): S1–23 (Aug. 1, 2005) (“Back”)

1034	DeJesus et al., “Abacavir versus Zidovudine Combined with Lamivudine and Efavirenz, for the Treatment of Antiretroviral-Naive HIV-Infected Adults,” <i>Clin. Infect. Dis.</i> 39(7): 1038–46 (2004) (“DeJesus”)
1035	Moyer, “Combined Tenofovir, Emtricitabine, Efavirenz May Be More Tolerable Than Standard First-Line HIV,” <i>Medscape Medical News</i> (Nov. 3, 2004), https://www.medscape.com/viewarticle/492968 (“Moyer”)
1036	Feinberg, “Tenofovir + Emtricitabine vs. AZT + 3TC,” <i>AIDS Clin. Care</i> 17(1): 7 (Jan. 1, 2005) (“Feinberg”)
1037	Mascolini, “Truvada Goes Toe-to-Toe with Combivir,” ICAAC Report: Evolving Antiretroviral Strategies, Conference Report for the National AIDS Treatment Advocacy Project (2004) (“Mascolini”)
1038	Gallant et al., “Efficacy and Safety of Tenofovir DF vs. Stavudine in Combination Therapy in Antiretroviral Naïve Patients: A 3-Year Randomized Trial,” <i>JAMA</i> 292(2): 191–201 (2004) (“Gallant”)
1039	Brenner et al., “HIV-1 Subtype C Viruses Rapidly Develop K65R Resistance to Tenofovir in Cell Culture,” <i>AIDS</i> 20(9): F9–F13 (Jun. 12, 2006) (“Brenner”)
1040	Food and Drug Administration, “Treatment Options for HIV, AIDS,” <i>FDA Consumer Magazine</i> , Nov.–Dec. 2004 (“FDA-2004”)
1041	De Clercq, “Emerging Anti-HIV Drugs,” <i>Expert Opin. Emerg. Drugs</i> 10(2): 241–73 (May 10, 2005) (“De-Clercq-2005”)
1042	Youle & Wainberg, “Pre-Exposure Chemoprophylaxis (PREP) as an HIV Prevention Strategy,” <i>J. Int’l Assoc. Physicians AIDS Care</i> 2(3): 102–5 (2003) (“Youle-JIAPAC”)
1043	Helene Gayle, Prepared Remarks, “Prevention Now! A Vision for the Future,” Bill & Melinda Gates Foundation (July 9, 2002), https://www.gatesfoundation.org/Media-Center/Speeches/2002/07/Helene-Gayle-2002-Prevention-Now (“Gayle”)

1044	Marilyn Chase, “Trials Will Test Whether AIDS Drug Can Also Prevent HIV,” Wall St. J., Dec. 4, 2003 (“Chase”)
1045	Tsai et al., “Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylrr-ethoxypropyl)adenine,” Science 270(5239): 1197–9 (1995) (“Tsai-1995”)
1046	Van Rompay et al., “Two Doses of PMPA Protect Newborn Macaques Against Oral Simian Immunodeficiency Virus Infection,” AIDS 12(9): F79–83 (1998) (“Van-Rompay-1998”)
1047	Otten et al., “Multiple Vaginal Exposures to Low Doses of R5 Simian-Human Immunodeficiency Virus: Strategy to Study HIV Preclinical Interventions in Nonhuman Primates,” J. Inf. Dis. 191(2): 164–73 (Dec. 9, 2004) (“Otten-2004”)
1048	Li et al., “Infection of Cynomolgus Monkeys with a Chimeric HIV-1/SIVmac Virus that Expresses the HIV-1 Envelope Glycoproteins,” J. Acquir. Immune Defic. Syndr. 5(7): 639–46 (1992) (“Li”)
1049	Gazzard et al., “The Combination of Tenofovir (TDF), Emtricitabine (FTC) and Efavirenz (EFV) has Significantly Greater Responses vs. Fixed-Dose Zidovudine/Lamivudine (CBV) and EFV in Antiretroviral Naive Patients: A 24-Week Preliminary Analysis,” ARV Update: 44th ICAAC Highlights (Dec. 2004), http://www.thebodypro.com/content/art34001.html (“Gazzard”)
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1051	Grant & Wainberg, “Chemoprophylaxis of HIV Infection: Moving Forward with Caution,” J. Infect. Dis. 194(7): 874–876 (Oct. 1, 2006) (“Grant-2006”)
1052	Subbarao et al., “Direct Stringency Comparison of Two Macaque Models (Single-high vs. Repeat-low) for Mucosal HIV Transmission

	Using an Identical Anti-HIV Chemoprophylaxis Intervention,” J. Med. Primatol. 36(4–5): 238–43 (2007) (“Subbarao-2007”)
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1054	Cohen, “Cambodian Leader Throws Novel Prevention Trial Into Limbo,” AIDS Research News of the Week, Science 305(5687): 1092 (2004) (“Cohen-2004”)
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1056	Torian et al., “HIV Type 2 in New York City, 2000–2008,” Clin. Infect. Dis. 51(11): 1334–42 (2010) (“Torian”)
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1058	Ruthie Blum, “Promoting Prophylaxis,” The Jerusalem Post (Jan. 11, 2007) (“Blum”)
1059	“Family Health International Receives Grant to Evaluate Once-Daily Antiretroviral as a Potential Method of HIV Prevention,” Bill & Melinda Gates Foundation (Oct. 28, 2002) (“Gates-Foundation”)
1060	Youle & Wainberg, “Could Chemoprophylaxis Be Used as an HIV Prevention Strategy While We Wait for an Effective Vaccine?” AIDS 17(6): 937–8 (2003) (“Youle-AIDS”)
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1062	Pope & Haase, “Transmission, Acute HIV-1 Infection and the Quest for Strategies to Prevent Infection,” Nat. Med. 9(7): 847–52 (2003) (“Pope”)

1063	Chakraborty, “Viral Burden in Genital Secretions Determines Male-to-Female Sexual Transmission of HIV-1: A Probabilistic Empiric Model,” <i>AIDS</i> 15(5): 621–7 (2001) (“Chakraborty”)
1064	Cohen & Pilcher, “Amplified HIV Transmission and New Approaches to HIV Prevention,” <i>J. Infect. Dis.</i> 191(9): 1391–3 (May 1, 2005) (“Cohen-Pilcher”)
1065	Fauci et al., “Immunopathogenic Mechanisms of HIV Infection,” <i>Ann Intern Med.</i> 124:654-663 (1996) (“Fauci-1996”)
1066	Rubbert & Ostrowski, “Pathogenesis of HIV-1 Infection,” in <i>HIV Medicine 2003</i> (Hoffmann & Kamps eds. 2003), 15–46 (“Rubbert”)
1067	Saag, “Candidate Antiviral Agents for Use in Postexposure Prophylaxis,” <i>Am. J. Med.</i> 102(5B): 25–31 (1997) (“Saag”)
1068	Angarano et al., “Transmission of Zidovudine-Resistant HIV-1 Through Heterosexual Contacts,” <i>AIDS</i> 8(7): 1013–4 (1994) (“Angarano”)
1069	Conlon et al., “Heterosexual Transmission of Human Immunodeficiency Virus Type-1 Variants Associated with Zidovudine Resistance,” <i>J. Infect. Dis.</i> 169(2): 411–5 (1994) (“Conlon”)
1070	Imrie et al., “Transmission of Human Immunodeficiency Virus Type-1 Resistant to Nevirapine and Zidovudine,” Sydney Primary HIV Infection Study Group, <i>J. Infect. Dis.</i> 175(6): 1502–6 (1997) (“Imrie”)
1071	Little et al., “Antiretroviral-Drug Resistance Among Patients Recently Infected With HIV,” <i>N. Eng. J. Med.</i> 347(6): 385–394 (2002) (“Little”)
1072	Pozniak et al., “British HIV Association (BHIVA) Guidelines for the Treatment of HIV-Infected Adults with Antiretroviral Therapy,” British HIV Association Writing Committee (July 2003) (“BHIVA”)
1073	Carpenter et al., “Antiretroviral Therapy for HIV Infection in 1998, Updated Recommendations of the International AIDS Society—USA Panel,” <i>JAMA</i> 280(1): 78–86 (1998) (“Carpenter”)

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1076	Department of Health and Human Services, “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents,” Panel on Clinical Practices for Treatment of HIV Infection (November 10, 2003) (“DHHS-2003”)
1077	Arribas et al., “The Combination of Tenofovir DF (TDF), Emtricitabine (FTC) and Efavirenz (EFV) Has Significantly Greater Response vs Fixed Dose Zidovudine/Lamivudine (CBV) And EFV in Antiretroviral Naïve Patients: A 24-Week Preliminary Analysis,” Abstract PL14.27th, Int’l Congress on Drug Therapy in HIV Infection, Glasgow (Nov. 14–18, 2004) (“Arribas”)
1078	Arguin & Magill, “For the Record: A History of Malaria Chemoprophylaxis,” Chapter 3: Infectious Diseases Related to Travel, https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/emfor-the-record-a-history-of-malaria-chemoprophylaxisem (“Arguin”)
1079	Dumond et al., “Non-Occupational Post-Exposure Prophylaxis and Antiretroviral Pharmacokinetics in the Male and Female Genital Tracts,” PRN 11(2): 10–16 (Oct. 2006) (“Dumond-PRN”)
1080	Rey et al., “Post-Exposure Prophylaxis After Occupational and Non-Occupational Exposures to HIV: An Overview of the Policies Implemented in 27 European Countries,” AIDS Care 12(6): 695–701 (2000) (“Rey”)
1081	Hosseini-pour et al., “Can Antiretroviral Therapy Be Used to Prevent Sexual Transmission of Human Immunodeficiency Virus Type 1?” Clin. Infect. Dis. 34(1): 1391–5 (2002) (“Hosseini-pour”)

1082	Guay et al., “Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: HIVNET 012 Randomised Trial,” <i>Lancet</i> 354(9387): 795–802 (1999) (“Guay”)
1083	Wade et al., “Abbreviated Regimens of Zidovudine Prophylaxis and Perinatal Transmission of the Human Immunodeficiency Virus,” <i>N. Engl. J. Med.</i> 339(20): 1409–14 (1998) (“Wade”)
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