Paper No. 1

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. IPR2019-01454
Patent No. 9,579,333
Filed: April 6, 2015

PETITION FOR *INTER PARTES* REVIEW

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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. 9,579,333 (Ex. 1003) ("'333 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 '333 Patent issued; namely: (i) IPR2019-01453 (challenging U.S. Patent No. 9,044,509); (ii) IPR2019-01455 (challenging U.S. Patent No. 9,937,191); and (iii) IPR2019-01456 (challenging U.S. Patent No. 10,335,423).

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

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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 organizations[3] published a report ("Cal-PrEP") describing an extension of the PEP regimen for "certain people at

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[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. 1011 ("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 '333 Patent encompass both regimens—certain claims require administration of TDF+FTC before an HIV exposure (i.e., PrEP), while others also cover administration after an HIV exposure (i.e., PEP). All or some of the '333 Patent claims are thus anticipated by the methods described in Cal-PrEP and in CDC-PEP, and all are obvious variants of both when considered together. Petitioner respectfully requests the Board to institute *inter partes* review of Claims 1-17 of the '333 Patent and cancel these claims.

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[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 '333 Patent. Neither Gilead, nor any party in privity with Gilead, has (i) filed a civil action challenging the validity of any claim of the '333 Patent; or (ii) been served a complaint alleging infringement of the '333 Patent more than a year prior to the present date. The '333 Patent also has not been the subject of a prior *inter partes* review. Gilead certifies that the '333 Patent is available for *inter partes* review.

Petitioner proposes three grounds:

(i) anticipation of Claims 1-17 by Cal-PrEP under 35 U.S.C. §102(b);

(ii) anticipation of Claims 12-17 under by CDC-PEP under 35 U.S.C. §102(b); and

(iii) obviousness of Claims 1-17 over CDC-PEP in view of Cal-PrEP under 35 U.S.C. §103.

Petitioner submits these grounds are not redundant. The two anticipation grounds address claims with distinct requirements that are anticipated for different reasons by the disclosures of Cal-PrEP and CDC-PEP. The anticipation grounds are not redundant with the proposed obviousness ground, which rests on a different rationale for unpatentability and is presented to respond to potential arguments Patent Owner may make regarding what the prior art teaches. And because all

three grounds rely on the same two prior art references 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 '333 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]:

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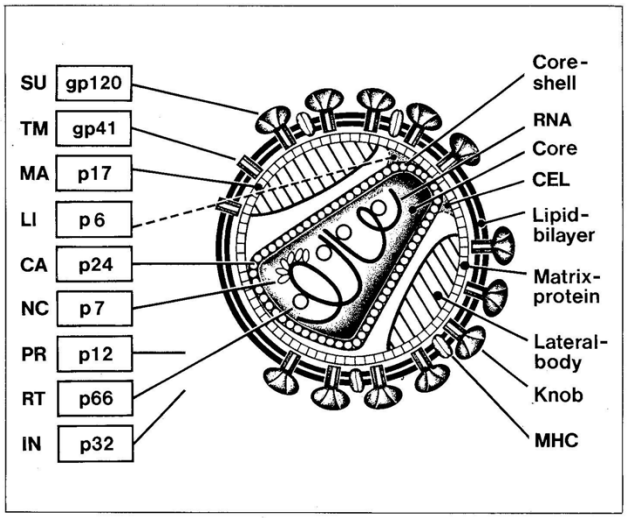
[5] *Great W. Cas. Co. v. Transpacific IP I Ltd.*, IPR2015-01912, Paper 10, 17-18 (P.T.A.B. Mar. 22, 2016).

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

[7] Ex. 1148 ("Gelderblom-1991"), 620.



HIV infections can result from an HIV "exposure," which occurs when virions are transferred via bodily fluids (e.g., semen or blood) to an individual.[8] To create a risk of infection, HIV must encounter CD4+ cells in the body and transform them to induce those cells to produce and release new virions, which can then transform other CD4+ cells. To do that, the virion binds to the CD4+ cell, which enables the HIV viral RNA to enter the cell.[9] Then, reverse transcriptase converts the viral RNA into viral cDNA, which enters the CD4+ cell nucleus and integrates into the host genome via the action of an integrase enzyme. The infected CD4+ cell then expresses the viral cDNA to produce viral protein precursors and additional copies of the HIV RNA. Protease enzymes then process the precursor

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8 Ex. 1009 ("Youle-Decl.") ¶¶43-44; Gelderblom-1991, 618-20.

9 Gelderblom-1991, 618, 630; Ex. 1149 ("Goldsby"), 452, Fig. 19-14.

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 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

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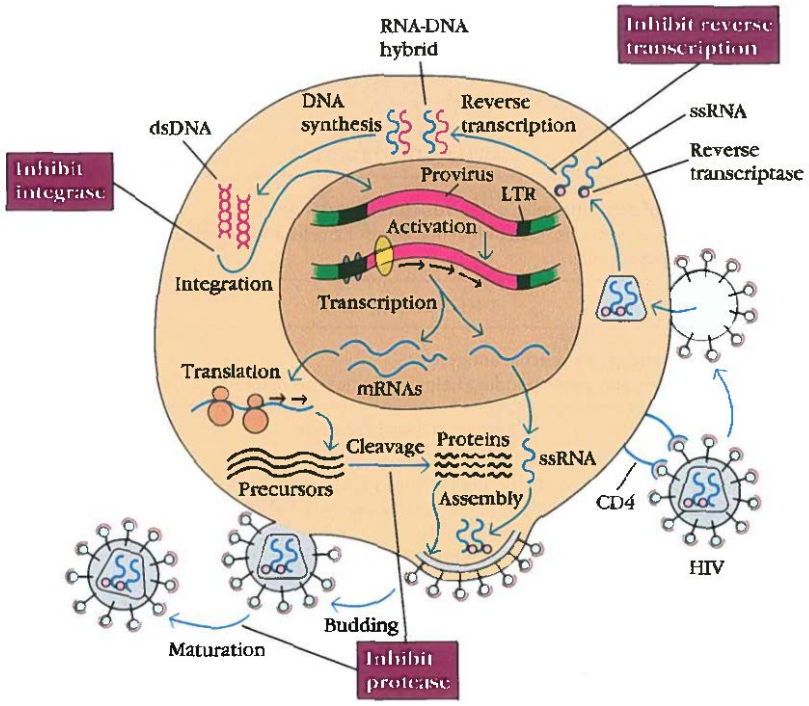
[10] Ex. 1061 ("Haase-2005"), 784; Ex. 1137 ("Miller"), 9217, 9222.

[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

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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 nucleo**t**ide reverse transcriptase inhibitors ("N**t**RTIs") such as tenofovir and tenofovir disoproxil fumarate (TDF)[18] and nucleo**s**ide 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

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[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 ("**N**NRTIs")—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 its requires HIV to acquire multiple mutations to overcome the inhibitory effect of the drugs.[22]

The CDC thus has recommended combinations of antiretrovirals for both treatment and prophylaxis of HIV since well before 2005, particularly two NRTIs[23] plus either a protease inhibitor (PI) or an NNRTI.[24] The two NRTIs are referred to

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[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.

as 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

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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]

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[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 properties[34]—a sufficiently long half-life to be suitable for once-daily dosing and no harmful interactions, which enables Truvada to provide a 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

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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, 11-12; 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]

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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 '333 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,

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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 ’333 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 ’333 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

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49 Youle-Decl. ¶16.

50 ’333 Patent, 3:13.

51 *Id.* 1:47-49.

52 *See, e.g., id.* 5:21-25 (“With conventional NRTI and NtRTI formulations, currently approved for HAART….”); *id.* 5:60-67 (NRTIs); *id.* 6:1-9 (NtRTIs); §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 '333 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 12 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"

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53 '333 Patent, 4:61-64; 1:58-62.

54 *Id.* 6:10-24.

55 *Id.* 7:42-8:10.

56 *See, e.g.*, Otten-2004, 164, 166; Ex. 1048 ("Li"), 639, 642; Youle-Decl. ¶¶211, 50.

57 '333 Patent, 9:47-10:21.

(Claim 1) or "an uninfected human that does not have the self-replicating infection" (Claim 12)) 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 12).

Both claims specify that TDF+FTC "is administered orally, subcutaneously or vaginally."

Despite having identical operative steps, the objective and desired results of the claimed methods are phrased differently:

Claim 1	*Claim 12*
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, including oral, subcutaneous, or vaginal administration]	[operative steps, including oral, subcutaneous, or vaginal administration]

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

2. <u>Proposed Constructions</u>

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

a. <u>"*[P]rotecting a primate host from a self-replicating infection*" (Claims 1-11) / "*[I]nhibiting establishment of a…self-replicating infection*" (Claims 12-17)</u>

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 12 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 12 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 12 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.

The specification reinforces these conclusions. For example, it states that "'protection' as used in the context of a host primate response to an

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[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).

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 degree of viral suppression of these different agents varies widely,[64] and that the

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[61] '333 Patent, 4:8-12. 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] '333 Patent, 2:14-19; 4:32-64, 5:60-6:9.

[63] *Id.* 6:25-46.

[64] *See* Youle-Decl. ¶¶83, 85, 88, 101.

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 an HIV infection when it becomes "a self-propagating" or "self-replicating retroviral" infection.[66] None of its passages addressing "establishment" proposes altering performance of the operative steps of Claim 12, 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.

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65 *See, e.g.*, '333 Patent, 9:58-60 ("Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed.") (emphasis added).

66 *Id.* 1:47-49 ("self-propagating"), 4:65-5:2 ("self-replicating"); *see also id.* 1:20-21.

67 *See, e.g.*, *id.* 9:58-60; footnote 64, *supra*.

Consequently, the preamble and "thereby" clauses in Claims 1 and 12 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 12)

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

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[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 '333 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" / "following 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 12 imposes no timing requirement;
- Claim 10 specifies that administration is "daily for several days, weeks or months both before and after an exposure";
- Claim 13 specifies administration is "prior to a potential exposure"; and

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[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] '333 Patent, 1:43-47.

- Claim 16 specifies administration "following potential exposure."

The '333 Patent uses "exposure" to refer to HIV viral particles being introduced into an individual in a manner that can result in infection.[73]

The '333 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 '333 Patent thus recognizes what was well-known in 2005—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 '333 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

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73 *Id.* 3:16-23, 28-32.

74 *Id.* 5:30-32 (emphasis added).

75 Cal-PrEP, 1; Youle-Decl. ¶144.

76 '333 Patent, 5:48-53 (emphasis added).

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

The '333 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.

Claim 12 makes no reference to the timing of an HIV exposure relative to administration, while Claims 13 and 16 specify administration before or after a "potential" exposure, respectively. The ordinary meaning of "potential" is that an

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77 Youle-Decl. ¶¶106-07, 253.

78 *See, e.g.*, '333 Patent, 1:67-2:3; 3:34-37.

event may, but may not necessarily, occur.[79] Claims 12, 13 and 16, thus, do not require an HIV exposure to actually occur after administration of the antiretroviral agents, which aligns with the method being prophylactic in nature.

Consequently, each of Claims 1, 12, 13 and 16 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 Claim 1 affirmatively requires an administration to precede an actual HIV exposure, with Claim 10 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 '333 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).

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[79] Ex. 1122 ("Random House Dictionary"), 1514 (defining "potential" as "possible, as opposed to actual").

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

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 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 document[84] 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

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81 Cal-PrEP, 2.

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.

and Reports (MMWR-RR) on January 21, 2005.[87] MMWR-RR has been an 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-

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87 Cal-PrEP, cover-1.

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

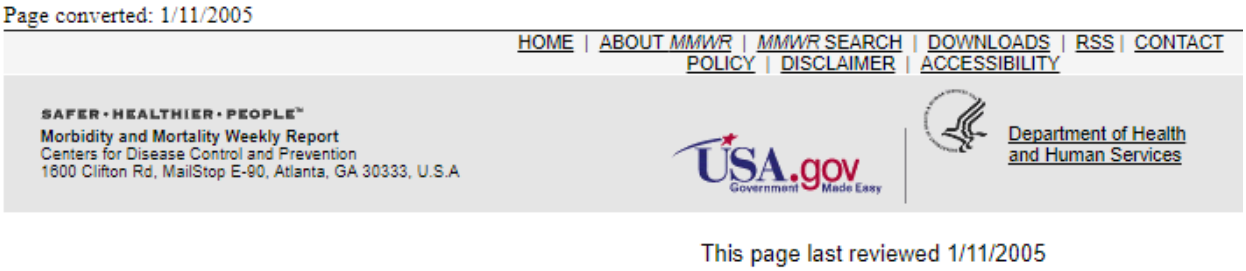
89 CDC-PEP, back-cover-2.

90 Ex. 1124 ("CDC-Archive"), 3.

91 Wayback-Decl.-II, 8.

92 Ex. 1128 ("UCSD-Decl.") ¶8.

PEP was made available on their website as from January 21, 2005,[93] and the CDC 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

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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,

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93 Ex. 1140 ("Kushan-Decl.") ¶¶6-11.

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

even without proof that doing so provided the specified therapeutic effect[95] 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 results specified in the claims of the '333 Patent, as the same

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[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).

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 provide fully enabling disclosures of those methods.

C. Claims 1-18 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]

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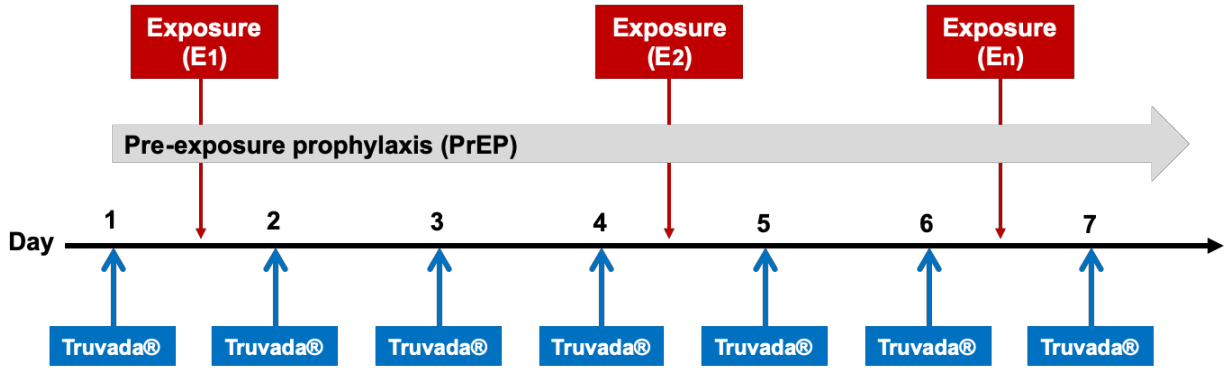
97 Cal-PrEP, 1, 3 (same).

98 *Id.* 11.

Cal-PrEP's regimen when followed by a high-risk individual who has multiple HIV exposures (E_1, E_2,…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

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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 12

Cal-PrEP anticipates Claims 1 and 12 of the '333 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 HIV 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 12 are not limiting, Cal-PrEP nonetheless describes a process that meets each.

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[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*" [12]

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 12.

c. *"[A]dministering…a combination comprising: (i) a pharmaceutically effective amount of emtricitabine…and (ii) a pharmaceutically effective amount of tenofovir or [TDF]" "wherein the pharmaceutically effective*

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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.

> *amount…is administered orally, subcutaneously or vaginally*" "*prior to the exposure*" [1]

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

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[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

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114 *Id.*, 11.

115 *Id.* (emphasis added).

116 Youle-Decl. ¶¶163, 227; Saag, 29.

PrEP regimens and stating, *inter alia*, that it is "a relatively safe agent with few 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

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117 Cal-PrEP, 11-12.

118 *Id.* 11 (emphasis added).

119 *Id.* 10-11.

120 Youle-Decl. ¶237.

FTC and 300 mg TDF,[121] the same doses in the FDA-approved single-agent 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 '333 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 '333 Patent also observes that "[p]referably, NRTI and NtRTI prophylactic

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

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

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

124 '333 Patent, 6:26-29.

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

dosing according to the present invention uses as a starting point the maximal recommended tolerated dosing levels for the given active agent combination associated with HAART treatment protocols."[126]

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

Cal-PrEP thus teaches orally administering Truvada 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 12 specify.

d. "Thereby" Clauses

While the "thereby" clauses of Claims 1 and 12 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 '333 patent disclosure say will protect the host from an HIV infection or will inhibit establishment of infection.

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126 '333 Patent, 6:41-46.

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 12 specify.

As Cal-PrEP describes every element of Claims 1 and 12, it anticipates both claims.

3. Claims 13 and 16

Claims 13 and 16 depend from Claim 12. Claim 13 specifies "*the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus*" while Claim 16 specifies administration "*following potential exposure of the primate host to the human immunodeficiency retrovirus*."

As noted in §V.C.2.c, a "potential exposure" does not require an actual HIV exposure to occur. Regardless, the PrEP regimen described in Cal-PrEP teaches providing antiretroviral therapy to uninfected individuals before and after an actual or potential HIV exposure. First, Cal-PrEP explains that "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."[128] Second, Cal-PrEP teaches that

[128] Cal-PrEP, 3 (emphasis added).

its PrEP regimen is to be followed for an extended period of time (e.g., 9 to 24 months)[129] by uninfected human subjects who, over that period, will engage in activities that cause multiple actual or potential HIV exposures (e.g., sex workers, men who have sex with men ("MSM"), intravenous drug users).[130]

Cal-PrEP thus teaches that HIV-uninfected high risk individuals on its regimen will be given doses of recommended TDF-based drugs (e.g., Truvada) on days that precede and follow days on which that individual is actually or potentially exposed to HIV, as Claims 13 and 16 specify, respectively.

4. Claims 2-3

Claim 2 specifies the primate host is an "*adult human*," while Claim 3 specifies the primate host is a "*male adult primate host*." Cal-PrEP indicates that candidates for prophylaxis include, *inter alia*, MSM, i.e., adult human males.[131]

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[129] Cal-PrEP describes clinical trials in which individuals are to be given a daily administration of a TDF-based drug for periods between 9 to 24 months. Cal-PrEP, 7-9; Youle-Decl. ¶203.

[130] Cal-PrEP, 1; *see also infra* Figures in §VI.E.1.

[131] Cal-PrEP, 4, 7, Table 1.

5. Claims 4 and 14

Claims 4 and 14 specify, respectively, that TDF+FTC are administered "*directly to a human in a combined single dosage formulation*" or "*into a single combination formulation*." Truvada is a tablet containing both TDF+FTC that is administered orally to humans. Cal-PrEP thus teaches administration of a single combination of TDF+FTC as Claims 4 and 14 specify.[132]

6. Claim 5

Claim 5 requires the "*immunodeficiency retrovirus*" to be a "*human immunodeficiency virus*." Cal-PrEP proposes the use of PrEP for HIV.[133]

7. Claim 6

Claim 6 specifies the "*human 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.[134] Cal-PrEP focuses on Californians, and thus would be understood as teaching use of chemoprophylaxis of HIV-1 infections.[135]

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132 *See id.* 11.

133 *Id.* 1.

134 Ex. 1056 ("Torian"), 1334; Ex. 1057 ("CDC-Surveillance"), 986.

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

8. Claims 7 and 17

Claim 7 specifies a "*rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus*," while Claim 17 specifies the exposure "*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…."[136] It also describes use of PrEP in "high-risk, HIV-negative MSM" and "[f]emale commercial sex workers."[137] 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.[138] 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 17.

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136 Cal-PrEP, 1.

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

138 *See* Youle-Decl. ¶143.

9. Claim 8

Claim 8 specifies "*administering 200 milligrams (mg) of emtricitabine and 300 mg of tenofovir disoproxil fumarate to a human host*." Cal-PrEP teaches use of Truvada in PrEP, which results in administration of 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate to the individual.[139]

10. 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*."[140]

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.[141] 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

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[139] Truvada®-Label, 21.

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

[141] 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).[142] Cal-PrEP also explains that "individuals take PrEP throughout their sexual lifetimes."[143]

Cal-PrEP also indicates that FDA-approved antiretroviral products are to be used, and identifies two such products: Viread (TDF) and Truvada (TDF+FTC).[144] A skilled person would understand from Cal-PrEP that these products should be used in their FDA-approved forms.[145]

Cal-PrEP thus anticipates Claim 9.

11. Claim 10

Claim 10 specifies 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, encompasses administrations that last "*several days*" before and after an exposure.

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142 Youle-Decl. ¶203.

143 Cal-PrEP, 22; Youle-Decl. ¶145.

144 Cal-PrEP, 11.

145 *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.[146] 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.[147] 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,[148] and are not to suspend taking antiretrovirals after an initial exposure.[149]

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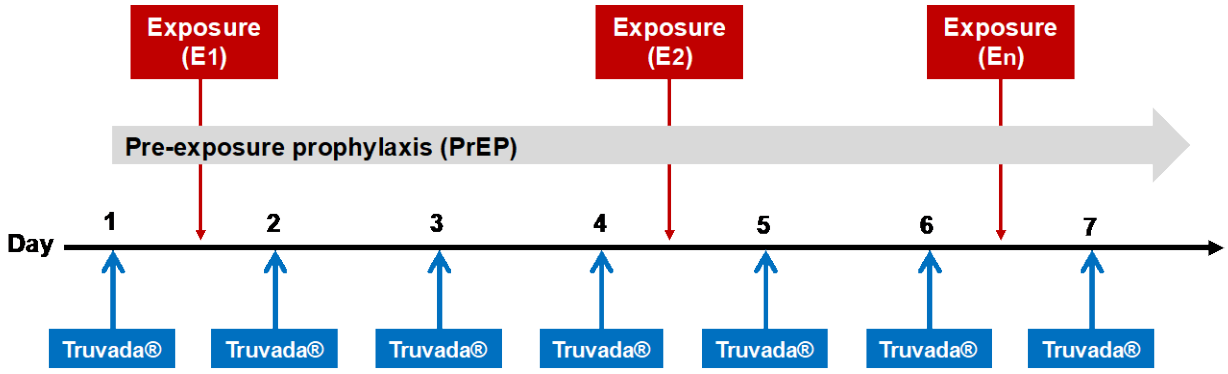
146 Cal-PrEP, 8-9, 12.

147 *Id.* 6-10; Youle-Decl. ¶149.

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

149 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).[150]



Cal-PrEP also cites Tsai-1995, a study in which antiretrovirals were administered for multiple days, both before and after exposure to the virus.[151]

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 exposure, as Claim 10 specifies.

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150 Youle-Decl. ¶164.

151 Tsai-1995, 1197.

12. 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.[152] Before February 2005, physicians considered the absence of viremia and seroconversion to demonstrate an absence of HIV infection.[153] 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.[154]

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.[155] A skilled person would understand

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152 *See supra* §VI.C.1.

153 Youle-Decl. ¶¶183, 166-67.

154 *Id.*; *see also* Ex. 1110 ("Fearon"), 26-29.

155 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.[156]

D. Claims 12-17 Are Anticipated by CDC-PEP

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 to prevent an HIV infection:

> A 28-day course of HAART[157] 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.[158]

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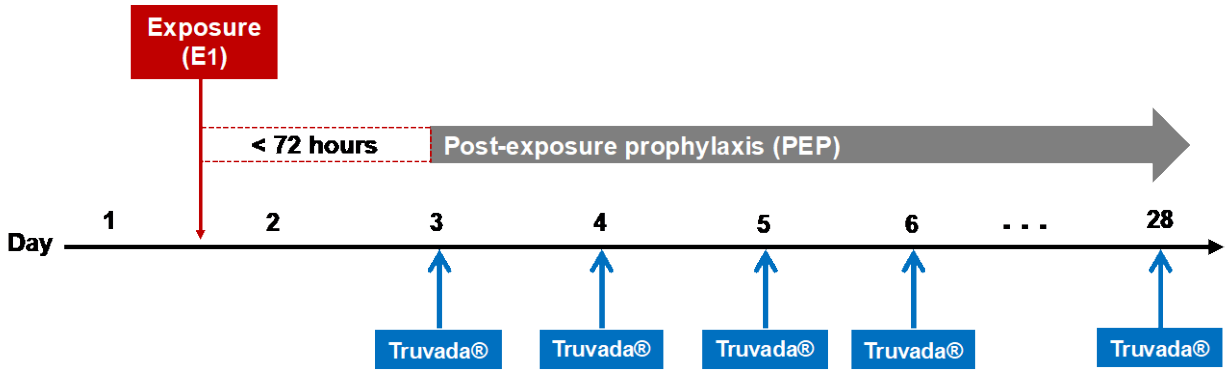
156 Youle-Decl. ¶¶166-67.

157 Highly active antiretroviral therapy (HAART) involves daily administrations of two or more antiretroviral agents. *See* CDC-PEP, 8; '333 Patent, 5:17-25.

158 CDC-PEP, 8.

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] PEP is illustrated below:[160]



CDC-PEP indicates the PEP regimen 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 exposures."[161] CDC-PEP also identifies non-clinical and clinical evidence supporting the efficacy of PEP in HIV prophylaxis:

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159 *Id.* 9-10.

160 Youle-Decl. ¶174.

161 CDC-PEP, 8.

> [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.[162]

CDC-PEP notes that PEP in an occupational setting "was associated with an 81% decrease in the risk for acquiring HIV."[163]

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."[164] CDC-PEP also explains PEP is warranted despite side-effects of antiretrovirals, explaining:

> Because HIV is an incurable transmissible infection that affects the quality and duration of life, HAART should be used to maximally

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162 *Id*. 2.

163 *Id*. 3.

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

> suppress local viral replication that otherwise might occur in the days after exposure and potentially lead to a disseminated, established infection.[165]

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."[166]

The use of combinations of antiretrovirals also was known to mitigate the risk of viral resistance.[167] In addition, physicians prefer backbones based on a single pill because they facilitate compliance, which is critically important in preventing HIV.[168]

2. Claim 12

a. Preamble

As described in §V.C.2.a, the preamble of Claim 12 is not limiting. Regardless, CDC-PEP teaches that the purpose of commencing a PEP regimen is

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165 *Id.* 8.

166 *Id.* 4.

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

168 Youle-Decl. ¶103.

to prevent the HIV infection from being established in an individual exposed to HIV, and emphasizes its effectiveness depends on how rapidly after the exposure it is commenced.[169] That is consistent with the understanding that HIV infections become established in an individual approximately three days after the HIV exposure. CDC-PEP thus teaches the same objective as the preamble of Claim 12.

b. *"[S]electing an uninfected human that does not have the self-replicating infection"*

CDC-PEP teaches selecting individuals that are HIV-negative for receiving PEP, explaining that PEP is to be used in humans who have an "exposure [that] represents a substantial risk for HIV transmission (Figure 1) and when the person seeks care within 72 hours of exposure."[170] A patient who is "at risk" does not yet have an established infection but may have been exposed to HIV.[171] CDC-PEP

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169 CDC-PEP, 8 ("[]PEP administered within 48-72 hours and continued for 28 days might reduce the risk for acquiring HIV infection after mucosal and other nonoccupational exposures. The sooner []PEP is administered after exposure, the more likely it is to interrupt transmission.").

170 *Id.*, 6, 8.

171 Youle-Decl. ¶43.

also teaches use of a "baseline" test to ensure the at-risk patient is not infected, followed by recurring testing to ensure that the prophylaxis is effective.[172]

c. *"[A]dministering…a combination comprising: (i) a pharmaceutically effective amount of emtricitabine…and (ii) a pharmaceutically effective amount of tenofovir or [TDF]" "wherein the pharmaceutically effective amount…is administered orally, subcutaneously or vaginally*"

CDC-PEP teaches that "[a] 28-day course of HAART is recommended for persons who have had nonoccupational exposure."[173] CDC-PEP notes "no evidence indicates that any specific antiretroviral medication...is optimal," but indicates certain regimens are "preferred."[174] CDC-PEP then recommends two "NNRTI-based" backbone regimens: efavirenz plus either (i) lamivudine plus zidovudine or (ii) emtricitabine plus tenofovir.[175]

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172 CDC-PEP, 7, 12; Youle-Decl. ¶¶182-83.

173 CDC-PEP, 8.

174 *Id*. 8.

175 *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).[176]

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,[177] specifying use of "1 tablet once daily 200 mg emtricitabine/300 mg tenofovir" in the form of Truvada.[178]

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176 Youle-Decl. ¶176.

177 CDC-PEP, 9, Table 2.

178 *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.[179] CDC-PEP also recommends use of only two agents—one NRTI and one NtRTI—in situations where the clinician or patient has concerns over the individual taking three antiretroviral agents.[180] Claim 12 encompasses administration of a third agent in addition to TDF and FTC by its use of "comprising" language.

A skilled person who follows CDC-PEP will administer Truvada *orally* to an HIV uninfected individual as required by the claims. Doing that orally administers to the individual the FDA-approved doses of 200 mg TDF and 300 mg

179 CDC-PEP, 8.

180 *Id.*, 8; Youle-Decl. ¶177.

FTC, which are pharmaceutically effective amounts of each agent.[181] The '333 Patent acknowledges these amounts are effective in preventing HIV infection.[182] CDC-PEP thus discloses the "administering" step of Claim 12.

CDC-PEP also teaches that commencing PEP using the recommended regimens as soon as possible after an exposure can prevent an HIV infection.[183] It credits animal studies and human clinical evidence as supporting this conclusion.[184] For example, it notes that prophylactic use of a less potent single-agent ARV (i.e., zidovudine) in a health-worker prophylaxis study "was associated with an 81% decrease in the risk for acquiring HIV."[185]

d. "Thereby" Clause

As explained in §V.C.2.a, Claim 12's "thereby" clause is not limiting. Nevertheless, CDC-PEP discloses methods that meet this requirement. Most notably, because CDC-PEP teaches administering a daily oral dose of the same,

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181 CDC-PEP, 10, Table 3; Youle-Decl. ¶¶174-75.

182 '333 Patent, 6:56-58, 7:44-60.

183 CDC-PEP, 2, 8.

184 *Id.* 8-9.

185 *Id.* 3.

FDA-approved and pharmaceutically effective amounts of TDF+FTC as the claims, it must yield the same result specified in the claims.[186] CDC-PEP also repeatedly states that PEP regimens are effective in preventing HIV infection if commenced early enough after an exposure. CDC-PEP thus discloses the "thereby" clause of Claim 12.

3. Claims 13 and 16

Claims 13 and 16 specify that administration is to occur "*prior to*" or "*following*" a "*potential*" exposure, respectively. As explained in §V.C.2.c, a "potential" exposure does not have to actually occur. Both claims are anticipated for the same reason that Claim 12 is anticipated.

CDC-PEP also expressly teaches administration of TDF+FTC following potential non-occupational HIV exposure, such as unprotected sex, and thus anticipates Claim 16.[187]

CDC-PEP further indicates that in a non-occupational setting, PEP is to be followed for at least a 28-day period.[188] CDC-PEP also explains that certain

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186 *Id.* 10, Table 3; Youle-Decl. ¶175.

187 CDC-PEP, 8.

188 *Id*.

categories of individuals engage in activity that may repeatedly expose them to HIV, and teaches that these "high-risk" individuals are to be counseled to refrain from such activities during the 28-day PEP regimen.[189] Such individuals, however, are likely to nonetheless engage in activities that may expose them to HIV during the 28-day PEP period.[190] Such individuals who have remained HIV-negative after a prior exposure will be administered TDF+FTC prior to the next (i.e., "a") potential exposure as Claim 13 specifies.

4. Claim 14

CDC-PEP teaches use of "Emtricitabine/tenofovir (Truvada)" as one of its two preferred PEP backbone regimens.[191] Truvada is formulated as a single dosage oral tablet.[192] CDC-PEP thus describes use of TDF+FTC that "*is compounded into a single combination formulation.*"

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189 *Id.* 8-9, 12; Youle-Decl. ¶180.

190 Youle-Decl. ¶135.

191 CDC-PEP, 10, Table 3.

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

5. Claim 15

CDC-PEP teaches use of HIV antibody tests (which assess seroconversion) and viral load tests (which assess persistent viremia) after the conclusion of prophylaxis to confirm that an infection has not occurred.[193] "HIV viral load" testing and "HIV antibody testing" are accepted ways of confirming a lack of persistent viremia and an absence of seroconversion.[194] Table 4 of CDC-PEP provides guidance on using these tests to confirm that prophylaxis was successful in a subject.[195] CDC-PEP thus teaches determining "*an inhibition of infection in the host" "by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.*"

6. Claim 17

CDC-PEP recommends a 28-day course of ARVs in the case of "[e]xposure of vagina, rectum….[w]ith…semen, vaginal secretions…."[196] These are all forms of exposure via sexual intercourse recited in Claim 17, which lists those exposures as alternatives. CDC-PEP thus teaches that "*the potential exposure to the human*

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193 CDC-PEP, 13, Table 4.

194 Youle-Decl. ¶183, 166-67; Fearon, 26.

195 CDC-PEP, 13, Table 4.

196 *Id*. 8, Fig. 1.

immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion."

E. Claims 1 to 17 Would Have Been Obvious

Patent Owner may contend that Cal-PrEP does not describe the method of Claims 1 to 17, 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 in the same doses to the same subjects for the same purpose as the contested claims, and thus necessarily describes the same process.[197]

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

[197] *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. 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.[198] As CDC-PEP teaches, commencing ARV administration as soon as possible after the HIV exposure is a key factor influencing success of that regimen.[199] Indeed, CDC-PEP emphasizes that "[t]he sooner []PEP is administered after exposure, the more likely it is to interrupt transmission."[200]

The skilled person also would have known that antiretrovirals "interrupt transmission" of HIV by actively suppressing HIV viral replication at the initial

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198 CDC-PEP at 8-12; Youle-Decl. ¶¶174, 179.

199 CDC-PEP, 8.

200 *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.

site of HIV exposure in the body.[201] That person likewise knew that antiretrovirals 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.[202] 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.[203] 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

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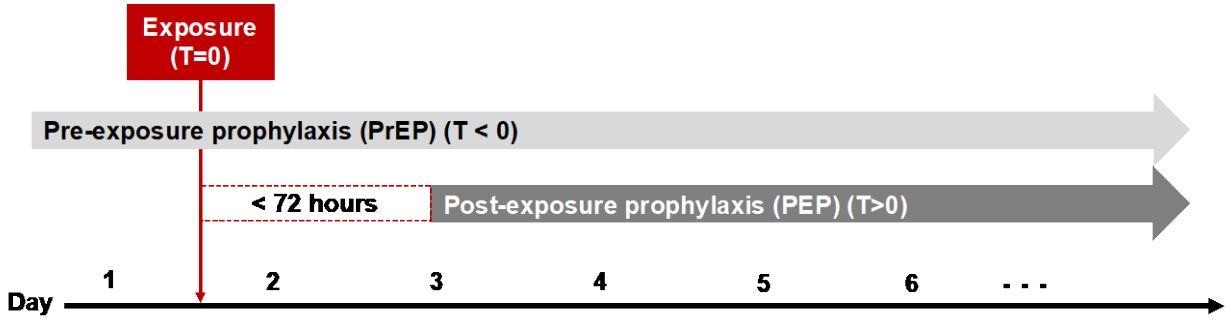
201 CDC-PEP, 8; Youle-Decl. ¶¶247-48.

202 Ex. 1079 ("Dumond-PRN"), 15; Youle-Decl. ¶¶244, 131.

203 Youle-Decl. ¶¶131-33; Saag, 28.

time immediately after (T>0) an HIV exposure to a time prior to that exposure (T<0).[204]



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,…E_n), both before and after taking daily doses of the antiretroviral agents, as illustrated below.[205]

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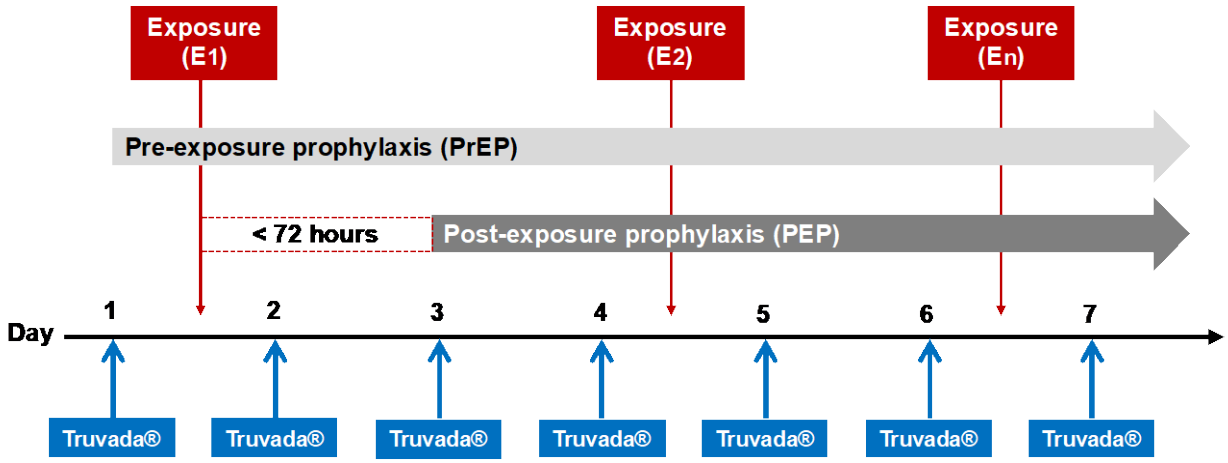
204 Youle-Decl. ¶¶245, 134.

205 *See id.*



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).[206] 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.[207] 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

206 *Id.* ¶136.

207 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.[208] 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.[209]

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.[210] Cal-PrEP also observes that behavioral interventions alone have not meaningfully

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208 Cal-PrEP, 10-11.

209 Youle-Decl. ¶146; Cal-PrEP, 6-10.

210 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.[211]

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.[212] Indeed, whether PrEP could reduce HIV infection rates in communities was one of the objectives of the clinical trials referenced in Cal-PrEP.[213]

2. 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"[214] or "optimal"[215] product to use in their respective chemoprophylaxis

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

212 Youle-Decl. ¶¶147, 149, 250.

213 *Id.* ¶261.

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

215 Cal-PrEP, 11; *see also supra* §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, [216] and to minimize risks of viral resistance that can arise from TDF or FTC monotherapy.[217]

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."[218] Truvada's clinical trial results showed no instances of viral resistance.[219] The skilled person thus would have understood that monotherapy-linked risks could be minimized by using Truvada, which combines TDF with FTC.[220]

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216 Moyer, 1; Youle-Decl. ¶237.

217 *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.

218 Cal-PrEP, 11 (emphasis added).

219 Moyer, 1.

220 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.[221] Consequently, a skilled person would have found it obvious to use Truvada in the PrEP regimen suggested by CDC-PEP and Cal-PrEP.

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

During examination, 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.[222] 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 12 are non-limiting.[223] And the

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

222 Ex. 1004 ("'333 File History"), 105-07.

223 *See supra* §V.C.2.a.

law only requires a reasonable expectation of success, not certainty, a standard more than met by the scientific evidence known before February 2005.[224]

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.[225]

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.[226] That observation also makes it clear that administering antiviral agents before an

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

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

226 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.[227] 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.[228] CDC-PEP, for example, refers to data showing an 81% reduction in infections in needle-stick settings using antiretroviral therapy with zidovudine.[229] CDC's own reliance on this evidence to support its PEP guidelines directly refutes Patent Owner's assertions during examination 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 uninfected

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227 Youle-Decl. ¶133; Saag, 28.

228 CDC-PEP, 2-4.

229 *Id.* 3.

individual.[230] 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.[231]

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. [232] The skilled person thus would have recognized that the way Truvada prevents HIV infection in the human body in the PEP regimen is identical

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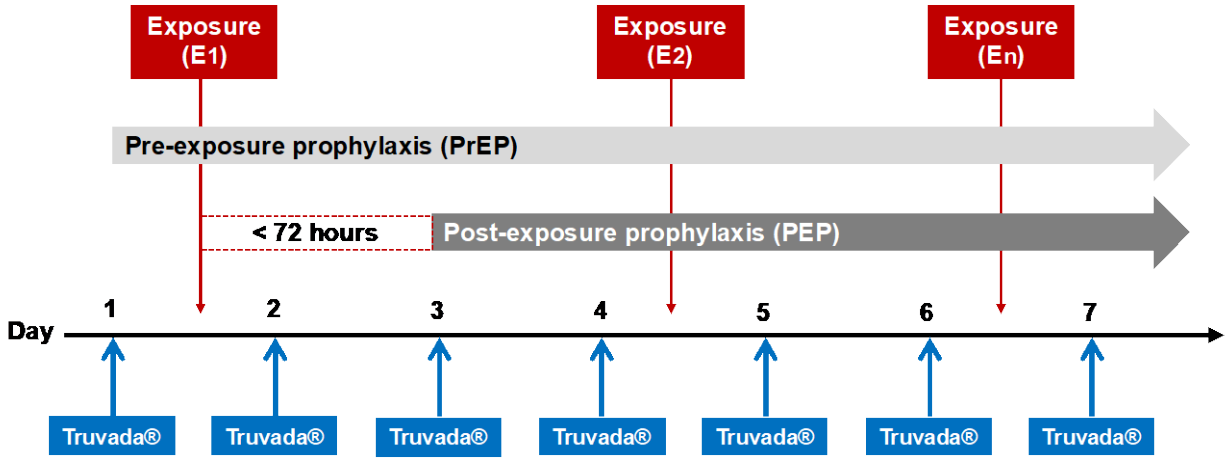
230 *See, e.g.*, '333 File History, 105 ("The art teaches that use of an anti-HIV agent to treat HIV infection does not reasonably predict the ability of that agent to protect against HIV infection.").

231 Moyer, 1.

232 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 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 PEP 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 E_2 or later).[233]



233 *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.[234]

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

234 *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 '333 Patent answers the questions supposedly raised in Cal-PrEP about the feasibility of PrEP. Most notably, the macaque studies reported in the '333 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.[235] 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.[236]

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

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235 *Id.* ¶¶262, 258.

236 *Id.* ¶¶251-52.

individuals to avoid high-risk activities while on the PEP regimen.[237] 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).[238] 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.[239]

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.[240] More than substantial evidence shows that to be true.

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237 CDC-PEP, 5.

238 Cal-PrEP, 27.

239 *Id.* 3.

240 Youle-Decl. ¶¶251, 253, 259.

d. HIV Chemoprophylaxis Was Not "Highly Unpredictable"

During examination of this and a related patent, Patent Owner claimed HIV chemoprophylaxis was "highly unpredictable" for various reasons.[241] 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.[242] 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.[243]

Second, Patent Owner portrayed Subbarao-2006 as showing that prophylaxis using TDF monotherapy in animal studies was unsuccessful, and, relying on a declaration from two of the inventors, claimed that "protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus," was significant and unexpected.[244] But skilled persons—including the CDC and the authors of

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241 Ex. 1002 ("'509 File History"), 82, 116-17; '333 File History, 105.

242 *Id.*; Youle-Decl. ¶¶83, 207.

243 '333 File History, 105.

244 *Id.* 106, 49-52.

Subbarao-2006—portrayed these same TDF monotherapy animal studies as being positive clinical results supporting PrEP.[245]

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."[246] 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.[247] 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.[248] 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

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245 Youle-Decl. ¶¶216-19, 233-36.

246 Ex. 1050 ("Subbarao-2006"), 907, 909; Youle-Decl. ¶217.

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

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

alone, and specifically recommended use of Truvada in PrEP.[249] And other contemporaneous publications cited other TDF-based PrEP animal studies as supporting the viability of TDF PrEP monotherapy in humans.[250] Thus, by February of 2005, it was expected (not unexpected) that TDF+FTC would be more effective than TDF monotherapy in PrEP.

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)*

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[249] Grant-2006, 875; *see also* Ex. 1053 ("Grant-2005"), 2170; Youle-Decl. ¶¶220-21; *supra* §IV.D.

[250] *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.

> *could reduce the risk of acquiring HIV infection* from sexual and drug-use exposures. [251]

The last assertion made by Patent Owner was that Cambodian TDF PrEP clinical trials were cancelled due to concerns over therapeutic efficacy.[252] That too is incorrect: one report identified concerns over trial participants being unfairly 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." [253]

And while Patent Owner asserted during examination that "the references, when considered in combination, do not disclose or suggest that a tenofovir/TDC [sic] can be combined with FTC" for PEP or PrEP,[254] that statement is demonstrably incorrect. As shown in §§VI.B-VI.D, CDC-PEP and Cal-PrEP each are based on the proposition that HIV prophylaxis with Truvada is effective. Critically, neither of those publications was provided to the Examiner during

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[251] Ex. 1123 ("CDC-2014"), 14 (emphasis added) (FN17 is Subbarao-2006).

[252] '333 File History, 105-06.

[253] Ex. 1054 ("Cohen-2004"), 1092.

[254] '333 File History, 104.

examination of the ’333 Patent and each is far more relevant to patentability than the references that were actually considered.

F. 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.[255] But to be pertinent to obviousness, the secondary considerations 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.”[256]

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 ’333 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-

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[255] Secondary considerations are irrelevant to anticipation.

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

integration" are likely to be effective.[257] Indeed, at best, the '333 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."[258] Gilead holds patents claiming once-daily oral formulations of TDF, FTC, and their combination, which cover all uses of the compounds.[259] 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

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257 *See, e.g.*, Cal-PrEP, 10-11.

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

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

and prophylaxis[260] and skilled persons proposed using it in large-scale PrEP trials.[261] 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.[262] And Truvada's more recent success in PrEP is not due to anything disclosed in the '333 Patent, but to the efforts of the CDC and Gilead to promote its use.

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

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

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

262 Youle-Decl. ¶241.

Board should not exercise its discretion under §325(d).[263] Neither Cal-PrEP nor CDC-PEP was cited during examination of the '333 Patent, and neither is cumulative or equivalent to the prior art used during its examination. Both references also are far more relevant than the art considered during examination.[264] This petition also proposes different grounds (including anticipation), and presents new evidence not considered by the Office—a declaration from Dr. Michael Youle (Ex. 1009), a noted expert in the field of HIV therapy and prevention.[265] This Petition therefore does not present the "same or substantially the same prior art or arguments" raised or considered during examination of the '333 Patent.

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[263] 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)).

[264] *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00486, Paper 10, 14-15 (P.T.A.B. July 15, 2015); *Becton Dickinson*, IPR2017-01586, Paper 8, 17-18; Trial Practice Guide, 29-30.

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

Patent Owner may nonetheless contend the Board should not institute trial because Cal-PrEP and CDC-PEP were considered during examination of a subsequently filed application, U.S. Application No. 15/406,344, which issued as U.S. Patent No. 9,937,191 (Ex. 1005) ("'191 Patent"). The issuance of the '191 Patent was in turn based on events that occurred during examination of U.S. Patent No. 9,044,509 (Ex. 1001) ("'509 Patent"). But the examination record of the '191 Patent reveals that "the Office erred in evaluating the asserted prior art" during its examination, which, if anything, justifies the Board not exercising its discretion under §325(d) here.[266]

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. The Examiner correctly observed that Cal-PrEP (also referred to as "Szekeres") identified (1) the need for biomedical approaches to HIV prevention including PrEP and that (2) TDF was

[266] Trial Practice Guide, 30 (factor 5).

well-suited for PrEP.[267] 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.[268]

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 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

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[267] Ex. 1006 ("'191 File History), 60. The Examiner consequently did not observe that Cal-PrEP also identified Truvada as one of two TDF options to use in PrEP.

[268] *Id.*, 60-61.

> dosage form: a tablet. The examiner indicates that such a claim would be allowable for reasons as set forth in the parent application.[269]

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."[270]

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.[271] Thus, the statement in the Examiner's interview summary form (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.

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269 *Id.*, 53 (emphasis added).

270 *Id.* 40 (emphasis added).

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

The examination record of the ’191 Patent 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 that the Examiner mistakenly equated the basis of the rejections 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—and relied on that mistake to find the ’191 Patent claims patentable. That mistake would warrant the Board not exercising its discretion in proceedings against the ’191 Patent. And, if the examination record of the ’191 Patent were somehow relevant to the earlier-examined ’333 Patent at issue in this petition, the Office’s later error there would (if anything) support the Board not exercising its §325(d) discretion here.

Consequently, because the patentability issues presented in this petition were never considered during examination of the ’333 Patent, the Board should not exercise its discretion under §325(d).

VIII. CONCLUSION

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

Dated: August 21, 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 13,918 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 21st 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

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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")
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1018	Coffin, "HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis, and Therapy," Science 267(5197): 483–9 (1995) ("Coffin")
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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")
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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/appletter/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")
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1032	Dando & Wagstaff, "Emtricitabine/Tenofovir Disoproxil Fumarate," Drugs 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," J. Acquir. Immune Defic. Syndr. 39(1): S1–23 (Aug. 1, 2005) ("Back")

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1038	Gallant et al., "Efficacy and Safety of Tenofovir DF vs. Stavudine in Combination Therapy in Antiretroviral Naïve Patients: A 3-Year Randomized Trial," JAMA 292(2): 191–201 (2004) ("Gallant")
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1052	Subbarao et al., "Direct Stringency Comparison of Two Macaque Models (Single-high vs. Repeat-low) for Mucosal HIV Transmission

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