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A PROGRAM OF YALE LAW SCHOOL AND THE YALE SCHOOL OF PUBLIC HEALTH

Title: Statement on CDC's Patents for PrEP
To: Global Health Justice Partnership, PrEP4All Collaboration
From: Christopher Morten
Date: March 12, 2019

I. Introduction

This statement presents preliminary legal analysis concerning certain patents owned by the U.S. government that concern prevention of infection by HIV and other retroviruses. This statement was prepared as part of my work with the [Global Health Justice Partnership](#) and the [Media Freedom & Information Access Clinic](#).

The Global Health Justice Partnership ("GHJP") is a joint initiative between [Yale Law School](#) and [Yale School of Public Health](#) that collaborates with NGOs domestically and worldwide to provide research and advocacy to support to critical health interventions. The Media Freedom & Information Access ("MFIA") Clinic is a student clinic at Yale Law School dedicated to increasing government transparency, defending the essential work of news gatherers, and protecting freedom of expression by providing pro bono legal services, pursuing impact litigation and developing policy initiatives.

I am a Research Scholar in Law at Yale Law School and a fellow of GHJP. I am also a Supervising Attorney and Clinical Lecturer in Law at MFIA. I am also the Staff Attorney at the [Collaboration for Research Integrity and Transparency](#) at Yale. I have practiced patent law for approximately six years, licensed first as a patent agent and then as a patent attorney (USPTO Reg. No. 69,974). My practice has included analysis of the validity, enforceability, and infringement of patents. I hold a B.A. in chemistry, a Ph.D. in organic chemistry, and a J.D.

The patents analyzed in this statement are U.S. Patent Nos. [9,044,509](#), [9,579,333](#), and [9,937,191](#). Each patent is entitled "Inhibition of HIV Infection through Chemoprophylaxis." Each patent describes and claims (that is, covers) methods of preventing retroviral infection (e.g., infection by HIV) in an uninfected patient by administering a combination of two drugs: (1) emtricitabine and (2) tenofovir or a chemical derivative of tenofovir. That is, each patent claims methods of pre-exposure prophylaxis ("PrEP") against HIV or another retrovirus with a combination of emtricitabine and tenofovir or a chemical derivative of tenofovir.

These patents appear to be relevant to the use of a prescription drug product, TRUVADA[®] (emtricitabine and tenofovir disoproxil fumarate) tablets. TRUVADA[®] tablets are approved by the Food and Drug Administration ("FDA") for preventing HIV infection. I



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conducted a preliminary analysis of the current FDA-approved [prescribing information for TRUVADA[®] tablets](#) published by Gilead Sciences, Inc. (“Gilead”), comparing the prescribing information to one of the claims of the patents.

II. Summary

Based on my preliminary analysis of U.S. Patent Nos. [9,044,509](#), [9,579,333](#), and [9,937,191](#), I have no reason to believe that the patents would be found invalid or unenforceable, if asserted in court. Based on my analysis of the TRUVADA[®] prescribing information in comparison to an exemplary claim of these patents, I have no reason to believe that use of TRUVADA[®] tablets according to its FDA-approved indication for preventing infection by HIV would not be found to infringe at least this exemplary patent claim. Infringement of a patent claim can create liability, including potential money damages owed to the patent owner, which in this case is the U.S. government. Below I explain my analysis in more detail.

III. The Evaluated Patents and the Scope of the Analysis Performed

The evaluated patents:

In November and December 2018, I conducted a preliminary analysis of U.S. Patent Nos. 9,044,509 (“the ’509 patent”), 9,579,333 (“the ’333 patent”), and 9,937,191 (“the ’191 patent”) (collectively, “the evaluated patents” or “CDC’s Patents for PrEP”). The analysis that follows is accurate, to the best of my knowledge, as of the date of this statement.

Each of the evaluated patents is entitled “Inhibition of HIV Infection through Chemoprophylaxis,” and each patent is assigned to the United States of America, as represented by the Secretary of the Department of Health and Human Services. Each patent identifies inventors Walid M. Heneine, Thomas M. Folks, Robert Janssen, Ronald Otten, and Jose Gerardo Garcia Lerma. According to a 2008 publication¹ coauthored by Heneine, Folks, Janssen, Otten, and Garcia Lerma, each of these individuals was affiliated with the Centers for Disease Control and Prevention (“CDC”) in Atlanta, Georgia. As such, the research underlying the evaluated patents appears to have been performed at the CDC, and I therefore refer to the evaluated patents as “CDC’s Patents for PrEP.”

Broadly speaking, each of CDC’s Patents for PrEP claims methods of protecting an uninfected subject from infection by an immunodeficiency retrovirus, e.g., HIV-1, by administering to the subject a combination of two drugs, (1) emtricitabine and (2) tenofovir or a tenofovir ester, e.g., tenofovir disoproxil fumarate, prior to exposure. That is, each of CDC’s

¹ [J. Gerardo Garcia-Lerma et al., *Prevention of Rectal SHIV Transmission in Macaques by Daily or Intermittent Prophylaxis with Emtricitabine and Tenofovir*, 5 PLoS Medicine e28 \(2008\).](#)



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Patents for PrEP generally claim methods of PrEP with a combination of emtricitabine and tenofovir, tenofovir disoproxil fumarate, or another tenofovir ester.²

Each claim of CDC's Patents for PrEP is distinct, but claim 1 of the '509 patent is broadly representative:

The invention claimed is . . . [a] process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:

- (a) selecting a primate host not infected with the immunodeficiency retrovirus, and
- (b) administering directly to an uninfected primate host a combination comprising:
 - i. a pharmaceutically effective amount of emtricitabine; and
 - ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate,

wherein the combination is administered prior to an exposure of the primate host to the immunodeficiency retrovirus, thereby protecting the primate host from infection with the immunodeficiency retrovirus, wherein the combination is administered orally.

The scope of the analysis performed:

I reviewed each of CDC's Patents for PrEP and its prosecution history. I also reviewed U.S. Provisional Patent Application No. 60/764,811, to which each of CDC's Patents for PrEP claims priority. I also reviewed certain foreign counterpart patents and patent applications of CDC's Patents for PrEP, including [European Patent No. 2,015,753](#) ("EP2015753"), and the prosecution and opposition histories of EP2015753. I also reviewed certain prior art references cited in the aforementioned prosecution and opposition histories. I also reviewed the [prescribing information for TRUVADA® \(emtricitabine and tenofovir disoproxil fumarate\) tablets, as revised 05/2018](#). This statement is limited by the scope of the analysis performed.³

² Pre-exposure prophylaxis ("PrEP"), in which a drug is given to a patient prior to exposure to an infectious virus to reduce the risk of infection, is distinct from post-exposure prophylaxis ("PEP"), in which a drug is given to a patient after exposure to an infectious virus to reduce the risk of infection.

³ This statement is not an opinion of counsel and cannot and should not be relied on as such. Among other things, I have not undertaken an in-depth analysis of construction of the claims of CDC's Patents for PrEP. Validity, enforceability, and infringement of the claims of CDC's Patents for PrEP depend on the construction of the claims. Moreover, the questions of enforceability and infringement are specific to a particular defendant. I have not reviewed all of the prior art references cited during prosecution of CDC's Patents for PrEP or their foreign counterparts or conducted independent searches for prior art that may be relevant to the claims of CDC's Patents for PrEP. Additional information that I have not considered relevant to the validity and/or enforceability of CDC's Patents for PrEP could come to light. The claims of CDC's Patents for PrEP could be cancelled or rendered or determined invalid and/or unenforceable in various ways, e.g., through statutory disclaimer, failure to pay maintenance fees, reexamination, post-grant proceeding at the Patent Trial and Appeal Board, or litigation in federal court.



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IV. Analysis of the Validity and Enforceability of CDC's Patents for PrEP

Filing, issuance, and expected expiration dates of CDC's Patents for PrEP:

In general, U.S. utility patents filed after Jun. 8, 1995, have a term of 20 years from their effective U.S. filing date, subject to any terminal disclaimers (which can decrease the patent term) or adjustments or extensions (which can increase the patent term).⁴ A patent's term can be cut short (i.e., a patent can expire early) if the patent holder fails to pay required a maintenance fee to the United States Patent and Trademark Office ("USPTO").⁵

According to information published on the first page of the patent, the '509 patent was filed on Jan. 31, 2007, and issued on Jun. 2, 2015. According to the [USPTO Public Patent Application Information Retrieval](#) ("Public PAIR") website⁶, the term of the '509 patent has been extended by an award of 1,562 days of Patent Term Adjustment ("PTA"). The '509 patent is not subject to any terminal disclaimer. Because it was filed on Jan. 31, 2007, and received an award of 1,562 days of PTA, May 12, 2031, is the expected expiration date of the '509 patent.

According to information published on the first page of the patent, the '333 patent was filed on Apr. 6, 2015, and issued on Feb. 28, 2017. The '333 patent is a continuation of the '509 patent, originally filed on Jan. 31, 2007. According to the Public PAIR website, the '333 patent has not received an award of PTA. Because Jan. 31, 2007, is the effective filing date of the '333 patent, Jan. 31, 2027, is the expected expiration date of the '333 patent.⁷

According to information published on the first page of the patent, the '191 patent was filed on Jan. 13, 2017, and issued on Apr. 10, 2018. The '191 patent is a continuation of the '333 patent, which is a continuation of the '509 patent, originally filed on Jan. 31, 2007. According to the Public PAIR website, the '191 patent has not received an award of PTA. Because Jan. 31, 2007, is the effective filing date of the '191 patent, Jan. 31, 2027, is the expected expiration date of the '191 patent.⁸

⁴ See, e.g., [Manual of Patent Examining Procedure § 2701 \(R-07.2015\)](#) ("Patent Term").

⁵ See, e.g., [Manual of Patent Examining Procedure § 2504 \(R-08.2017\)](#) ("Patents Subject to Maintenance Fees").

⁶ <https://portal.uspto.gov/pair/PublicPair>.

⁷ According to the Public PAIR website, the '333 patent is terminally disclaimed to the '509 patent, and the '191 patent is terminally disclaimed to both the '509 and '333 patents. Because the expected expiration date of the '509 patent (May 12, 2031) is after the date on which the basic 20-year terms of the '333 and '191 patent end (Jan. 31, 2027), these terminal disclaimers have no effect on the expected expiration dates of the '333 and '191 patents.

⁸ See n.7, *supra*.



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According to both the USPTO Public PAIR and the USPTO Patent Maintenance Fees⁹ websites, none of CDC's Patents for PrEP has expired for nonpayment of maintenance fees.

Analysis of enforceability:

I have no reason to believe that CDC's Patents for PrEP are unenforceable for any reason, e.g., due to inequitable conduct during prosecution of the patents.

Analysis of validity:

As an initial matter, under U.S. law, CDC's Patents for PrEP would be presumed valid if asserted in federal court.¹⁰

Under U.S. law, an inventor may typically obtain a patent on a new and useful process, such as a method of using a drug (or combination of drugs),¹¹ so long as the patent complies with the conditions and requirements of patentability. Among the most important of these conditions and requirements are novelty ([35 U.S.C. § 102](#)); nonobviousness ([35 U.S.C. § 103](#)); and enablement, written description, and definiteness ([35 U.S.C. § 112](#)).¹² The novelty condition of § 102 generally prohibits patenting of subject matter that is already known to the public. The nonobviousness condition of § 103 generally prohibits patenting of subject matter that is merely an obvious (e.g., trivial or predictable) variation of subject matter that is already known to the public.¹³ The enablement requirement of § 112 requires a patent to disclose the claimed subject matter in sufficient detail for a person of ordinary skill in the relevant art (i.e., the relevant field) to make and use the invention. The written description requirement of § 112 requires a patent to disclose the claimed subject matter in such a way that demonstrates that the inventors actually possessed the claimed subject matter at the time the patent was filed. The definiteness requirement of § 112 requires a patent to clearly and distinctly define the claimed subject matter.

⁹ <https://fees.uspto.gov/MaintenanceFees>.

¹⁰ [35 U.S.C. § 282\(a\)](#).

¹¹ See [35 U.S.C. § 101](#) ("Whoever invents or discovers any new and useful process . . . may obtain a patent therefor, subject to the conditions and requirements of this title."); see also, e.g., *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1302 (2012) (approving of patents covering "a new way of using an existing drug").

¹² The America Invents Act of 2011 ("AIA") amended the Patent Act and modified the text of §§ 102 and 103. Because CDC's Patents for PrEP have an effective filing date of Jan. 31, 2007, prior to the effective date of the AIA (March 16, 2013), they are subject to pre-AIA §§ 102 and 103. I have accordingly cited and quoted pre-AIA versions of §§ 102 and 103. This paragraph's high-level characterization of the novelty and nonobviousness requirements of §§ 102 and 103 holds true for both pre- and post-AIA versions of these provisions.

¹³ See, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).



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Each of CDC's Patents for PrEP was examined by a patent examiner at the USPTO for compliance with the conditions and requirements of patentability, including all the aforementioned: novelty, nonobviousness, enablement, written description, and definiteness. During the examination process (also known as the patent prosecution process) of the three patents, the examiner issued office actions rejecting various claims on the bases of alleged lack of novelty and alleged obviousness, but these rejections were overcome, and each patent was granted.

As to novelty (§ 102), the examiner rejected certain claims for alleged lack of novelty during early stages of examination of the application that became the '509 patent. However, the examiner later withdrew these rejections in light of amendments made to the claims, which specified that the claimed methods require the use of emtricitabine or another compound selected from a short list of anti-HIV drugs.¹⁴ The examiner concluded that "the rejections under 35 U.S.C. [§] 102 set [forth] in [the] prior office action [are] withdrawn in view of the amendments."¹⁵ The examiner did not make further rejections based on lack of novelty during prosecution of the '509, '333, and '191 patents.

As to nonobviousness (§ 103), the examiner rejected certain claims of the applications that became the '509, '333, and '191 patents for alleged obviousness, in view of what was known in the prior art. However, the examiner ultimately withdrew all rejections under § 103 and allowed the claims of these patents. For example, in the Notice of Allowance for the '509 patent, dated Jan. 8, 2015, the patent examiner concluded that the claimed methods of prophylaxis are not obvious in view of the prior art, noting that "chemoprophylaxis for viral infections in general, and HIV infection, [is] highly unpredictable," and that "the [patent] application shows that the combination [of emtricitabine and tenofovir or a tenofovir ester] has superior effect as compared to tenofovir alone in animal model[,] and evidence[,] on the record has shown the claimed combination has clinically significant results, which would not have been expected in view [of] the prior art as a whole."¹⁶ The examiner noted evidence that as of the relevant priority date of CDC's Patents for PrEP, others had tried and failed to use a drug proven effective in treating existing HIV infections (maraviroc) for effective oral PrEP in HIV-naïve

¹⁴ To be more specific, the amendment, entered on September 23, 2010, specified that the claimed methods require the use of a nucleoside reverse transcriptase inhibitor, where the nucleoside reverse transcriptase inhibitor is emtricitabine, lamivudine, zalcitabine, azidothymidine, didanosine, stavudine, abacavir, or pharmaceutically acceptable derivatives thereof. *See* Prosecution History of U.S. Patent No. 9,044,509, Request for Continued Examination (RCE) and Amendment dated September 23, 2010. The claims of the '509 patent were narrowed further through subsequent prosecution to require the use of emtricitabine specifically (in combination with tenofovir or a tenofovir ester, e.g., tenofovir disoproxil fumarate). The claims of the '333 and '191 patents likewise require the use of emtricitabine specifically.

¹⁵ Prosecution History of U.S. Patent No. 9,044,509, Non-final Rejection dated May 23, 2013, at 5.

¹⁶ Prosecution History of U.S. Patent No. 9,044,509, Notice of Allowance dated Jan. 8, 2015, at 4.



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subjects.¹⁷ The examiner further noted evidence that when tenofovir disoproxil fumarate was tested on its own, rather than in combination with emtricitabine, in animal studies, it had proven ineffective for use as PrEP.¹⁸ The examiner also credited a 2010 New England Journal of Medicine article by Grant et al., which reported the results of a clinical trial on the efficacy of once-daily administration of a combination of emtricitabine and tenofovir disoproxil fumarate as compared with placebo for the prevention of HIV acquisition among men and transgender women who have sex with men and showed that trial subjects who had detectable levels of the drugs in their blood reduced their risk of HIV infection by 92-95%.¹⁹ The examiner noted the same evidence when allowing the '333 and '191 patents.

As part of my analysis of the validity of CDC's Patents for PrEP, I reviewed a foreign patent: [EP2015753](#). EP2015753 is a European Patent counterpart to CDC's Patents for PrEP, with claims of similar scope.²⁰ EP2015753 was challenged by Generics (UK) Limited (trading as Mylan), a division of the global generic pharmaceutical company Mylan, in an intensive, multi-year *inter partes* procedure known as an opposition.²¹ According to the European Patent Register, EP2015753 survived the opposition and is in force today.²²

I have reviewed certain prior art references cited by the examiner during prosecution of CDC's Patents for PrEP and have also reviewed additional references cited by Mylan in its opposition to EP2015753. Based on the entirety of my review, I have no basis on which to disagree with the conclusions of the USPTO and European Patent Office that the claims of CDC's Patents for PrEP and the related claims of EP2015753 are valid. Based on the entirety of my review, I have no reason to believe that the claims of CDC's Patents for PrEP would be found invalid if asserted.

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.* (citing [Robert M. Grant et al., Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men](#), 363 N. Eng. J. Med. 2587 (2010)).

²⁰ EP2015753 identifies as "Proprietor" (owner) "[t]he Government of the United States of America, as represented by the Secretary, Department of Health & Human Services[,], Atlanta, Georgia 30341 (US)." EP2015753 claims priority to [International \(PCT\) Patent Application No. PCT/US2007/002926, published as WO 2007/092326](#), which similarly identifies the patent applicant as the Department of Health & Human Services and the Technology Transfer Office of the CDC.

²¹ <https://register.epo.org/application?number=EP07763090>.

²² *Id.* Claims of EP2015753 were amended during the opposition procedure.



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V. Analysis of Infringement of CDC’s Patents for PrEP

TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) tablets are a drug product marketed by Gilead. I have compared the instructions on use of TRUVADA® tablets provided in the TRUVADA® prescribing information, as dated “Revised: 05/2018,” to the claims of CDC’s Patents for PrEP, to analyze whether use of TRUVADA® tablets according to Gilead’s instructions may infringe CDC’s Patents for PrEP. An exemplary comparison between the TRUVADA® prescribing information and the elements of claim 1 of the ’509 patent is presented in the table below.

Claim 1 of the ’509 patent	Instructions in the TRUVADA® prescribing information
A process of protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus comprising:	TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. (Section 1.2)
(a) selecting a primate host not infected with the immunodeficiency retrovirus, and	<p>Individuals must have a negative HIV-1 test immediately prior to initiating TRUVADA for HIV-1 PrEP [see Dosage and Administration (2.2)]. (Section 1.2)</p> <p>Screen all patients for HIV-1 infection before initiating TRUVADA for HIV-1 PrEP and at least once every 3 months while taking TRUVADA [see Indications and Usage (1.2), Contraindications (4) and Warnings and Precautions (5.2)]. (Section 2.2)</p>
(b) administering directly to an uninfected primate host a combination comprising: i. a pharmaceutically effective amount of emtricitabine; and ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate,	<p>The dosage of TRUVADA in HIV-1 uninfected adults and adolescents weighing at least 35 kg is one tablet (containing 200 mg of FTC [emtricitabine] and 300 mg of TDF [tenofovir disoproxil fumarate]) once daily taken orally with or without food [see Clinical Pharmacology (12.3)]. (Section 2.5)</p> <p>TRUVADA tablets are fixed-dose combination tablets containing emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). (Section 11)</p>



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Claim 1 of the '509 patent	Instructions in the TRUVADA® prescribing information
wherein the combination is administered prior to an exposure of the primate host to the immunodeficiency retrovirus, thereby protecting the primate host from infection with the immunodeficiency retrovirus,	<p>TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. Individuals must have a negative HIV-1 test immediately prior to initiating TRUVADA for HIV-1 PrEP [see Dosage and Administration (2.2)]. (Section 1.2)</p> <p>Screen all patients for HIV-1 infection before initiating TRUVADA for HIV-1 PrEP and at least once every 3 months while taking TRUVADA [see Indications and Usage (1.2), Contraindications (4) and Warnings and Precautions (5.2)]. (Section 2.2)</p>
wherein the combination is administered orally.	<p>The dosage of TRUVADA in HIV-1 uninfected adults and adolescents weighing at least 35 kg is one tablet (containing 200 mg of FTC [emtricitabine] and 300 mg of TDF [tenofovir disoproxil fumarate]) once daily taken orally with or without food [see Clinical Pharmacology (12.3)]. (Section 2.5)</p> <p>TRUVADA tablets are for oral administration (Section 11)</p>

As reflected in the table above, it appears that use of TRUVADA® tablets as instructed by the TRUVADA® prescribing information meets each and every limitation of claim 1 of the '509 patent. Therefore, if claim 1 of the '509 patent were asserted and were found to be valid and enforceable, I have no reason to believe that a court would not find that use of TRUVADA® tablets, as instructed by the TRUVADA® prescribing information provided by Gilead, directly infringes that claim.

Infringement of a patent claim can create liability, including the potential to owe money damages to the patent owner to compensate for the infringing activity. Here, the patent owner is the U.S. government. Should the U.S. government decide to enforce claim 1 of the '509 patent, or other, similar claims of CDC's Patents for PrEP, it appears to me that the U.S. government could possibly be entitled to collect money damages.