No. 2024-2069

IN THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

UNITED STATES,
Plaintiff-Appellant,

v.

GILEAD SCIENCES INC. INC., GILEAD SCIENCES IRELAND UC,
Defendants-Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE, IN 1:19-CV-2103, JUDGE MARYELLEN NOREIKA

BRIEF OF THE PLAINTIFF-APPELLANT, THE UNITED STATES

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PATENT CLAIMS AT ISSUE

U.S. Patent No. 9,579,333: Claim 13, which depends from Claim 12.

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human.

13. The process of claim 12, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

U.S. Patent No. 9,937,191: Claim 18, which depends from Claims 13 and 17:

13. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine in a tablet; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir disoproxil fumerate in a tablet;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

17. The process of claim 13, wherein:

(i) the pharmaceutically effective amount of emtricitabine; and

(ii) the pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate; are formulated in a single tablet.

18. The process of claim 17, wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disproxil fumarate.

U.S. Patent No. 10,335,423: Claim 18, which depends from Claim 12:

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir prodrug;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to potential exposure the human to the human immunodeficiency retrovirus.

18. The process of claim 12, wherein the combination comprises the tenofovir prodrug.

TABLE OF CONTENTS

I. STATEMENT OF RELATED CASES....1

II. STATEMENT OF APPELLATE JURISDICTION....3

III. STATEMENT OF THE ISSUES PRESENTED FOR REVIEW....3

IV. INTRODUCTION....4

V. STATEMENT OF THE CASE....6

A. The Parties....6

B. CDC's Groundbreaking Research Led to the Patents-In-Suit....7

1. Early Single-Drug PrEP Research Showed Limited Efficacy....8

2. The Inventors Combined Multiple Drugs to Prevent HIV Infection....10

C. FDA Approved Truvada for PrEP, but Gilead Was Not Interested....12

D. The Patents-in-Suit All Include an Efficacy Limitation....14

E. When the Government Sought to License These Patents to Gilead, Gilead Refused and Initiated PTAB Proceedings....15

F. Proceedings Below....18

1. Pretrial Rulings....19

a. The district court denied the Government's motion of no anticipation based on the Conant public use....19

b. The district court permitted Gilead to introduce evidence of the Material Transfer Agreements,

even though Gilead had notice of the Patents-in-Suit prior to infringement.....21

c. The district court excluded evidence of Gilead's failed IPR proceedings and the PTAB's analysis of the PEP Guidelines 23

2. Trial Proceedings 24

3. Post-Trial Proceedings 25

VI. SUMMARY OF THE ARGUMENT 27

VII. ARGUMENT 30

A. Standard of Review 300

B. The District Court Erred in Its Anticipation Analysis 33

1. The "Thereby" Clause Requires the Host To Remain Negative Based on Testing.....34

2. No Source of Purported Public Knowledge or Public Use Disclosed That the Claimed Methods Resulted in a Host Remaining Negative Based on Testing.....35

a. Dr. Conant's Purported Public Use Lacked Corroboration.....35

b. There Was No Public Knowledge of the Efficacy Step Based on Dr. Grant.....39

i. There Was No Disclosure of the Efficacy Step. 39

ii. Gilead's expert did not address the efficacy limitation.....42

iii. The district court Legally Erred in Ruling that Dr. Grant's Documents Were Public. 43

c. Uncorroborated Testimony of Dr. Kaldor's Purported Knowledge of "Truvada for PrEP" Nowhere Disclosed the Efficacy Limitation 46

C. The Obviousness Verdict Is Unsupported by Substantial Evidence and Tainted by Nonqualified Prior Art and Improperly Excluded Evidence. 47

1. None of Gilead's three prior art references teach or suggest the claimed efficacy provided by the "thereby" clause. 47

a. There is no express teaching or suggestion in the primary prior art references of the PrEP efficacy required by the "thereby" clause. 48

b. The district court further erred in evaluating motivation to combine and reasonable expectation of success. 54

c. There is no teaching or suggestion of the "thereby" clause in the background knowledge and teachings presented at trial.....544

D. A New Trial Is Warranted Based on Gilead's Use of Nonqualified Art and the District Court's Erroneous Evidentiary Rulings. 57

1. Gilead's Reliance on Nonqualified Prior Art Justifies a New Trial. 57

a. Dr. Flexner Relied On Nonqualified Prior Art Throughout His Obviousness Testimony. 57

b. The prejudice created by the nonqualified art was exacerbated by the jury instructions. 58

2. A new trial on obviousness is warranted based on excluded evidence regarding Gilead's failed IPR proceedings. 59

E. The District Court Erred In Allowing Irrelevant and Prejudicial Evidence Regarding the Government's Alleged Breach of the MTAs 62

F. Gilead Presented Insufficient Evidence that "Tenofovir Prodrug" in Claim 18 of the '423 Patent Is Not Enabled. 65

VIII. CONCLUSION 69

TABLE OF AUTHORITIES

Acumed LLC v. Advanced Surgical Services, Inc.
561 F.3d 199 (3d Cir. 2009) 30, 39, 43, 46

Allergan, Inc. v. Sandoz Inc.,
726 F.3d 1286 (Fed. Cir. 2013) 53

Amgen Inc. v. Sanofi,
598 U.S. 594 (2023).....32

Arendi S.A.R.L. v. Apple Inc.,
832 F.3d 1355 (Fed. Cir. 2016) 56

AstraZeneca LP v. Apotex, Inc.,
633 F.3d 1042 (Fed. Cir. 2010) 42

ATEN Int'l v. Uniclass Technology Co.,
932 F.3d 1364 34

Beachcombers, Int'l, Inc. v. WildeWood Creative Products, Inc.,
31 F.3d 1154 (Fed. Cir. 1994) 53

Bruning v. Hirose,
161 F.3d 681 (Fed. Cir. 1998) 65, 66

Cantrell v. Wallick,
117 U.S. 689 (1886).....39

Cephalon v. Watson,
707 F.3d 1330 (Fed. Cir. 2003) 67

Cordis Corp. v. Boston Scientific Corp.,
561 F.3d 1319 (Fed. Cir. 2009) 44, 45

Ecolochem, Inc. v. S. Cal. Edison Co.,
227 F.3d 1361 (Fed. Cir. 2000) 31, 42

Finnigan Corp. v. Int'l Trade Comm'n,
180 F.3d 1354 (Fed. Cir. 1999) 39

Fleming v. Escort, Inc.,
1774 F.3d 1371, 1377 (Fed. Cir. 2014) 31

Gilead Sciences, Inc. v. The United States of America,
20-499C (Fed. Cl.) 1

Gilead Scis., Inc. v. United States,
163 Fed. Cl. 104 (2022) 23

Graham v. John Deere Co.,
383 U.S. 1 (1966) 47

Juicy Whip v. Orange Bang,
292 F.3d 728 (Fed. Cir. 2002) 37

K/S Himpp v. Hear-Wear Techs, LLC,
751 F.3d 1362 (Fed. Cir. 2014) 56

Koito Mfg. Co. v. Turn-Key-Tech, LLC,
381 F.3d 1142 (Fed. Cir. 2004) 50

Lazare Kaplan Int'l v. Photoscribe Techs., Inc.,
628 F.3d 1359, 1374 (Fed. Cir. 2010) 38

Leonard v. Stemtech Int'l Inc.,
834 F.3d 376 (3d Cir. 2016) 33

MobileMedia Ideas, LLC v. Apple, Inc.,
780 F.3d 1159 (Fed. Cir. 2015) 30

Medichem, S.A. v. Rolabo, S.L.,
437 F.3d 1157 (Fed. Cir. 2006) 48

NexStep, Inc. v. Comcast Cable Commc'ns, LLC, 119 F.4th 1355,
1374 (Fed. Cir. 2024) 68

Pannu v. Iolab Corp.,
155 F.3d 1344 (Fed. Cir. 1998) 31

Par Pharma., Inc. v. TWI Pharmas, Inc.,
773 F.3d 1186 (Fed. Cir. 2014) 31, 32, 48, 54

Pfizer, Inc. v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007) 48

Rhone-Poulenc Agro, S.A. v. DeKalb Genetics Corp.,
272 F.3d 1335 (Fed. Cir. 2001) (cert. granted, judgment vacated and remanded on other grounds, 538 U.S. 974 (2003) and opinion modified and reinstated, 345 F.3d 1366 (2003)) 65

Sandt Tech., Ltd. v. Resco Metal and Plastics Corp.,
264 F.3d 1340, 1350 (Fed. Cir. 2001) 38

Schumer v. Lab. Computer Sys., Inc.,
308 F.3d 1304 (Fed. Cir. 2002) 68

Siemens Medical Solutions USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.,
637 F.3d 1269 (Fed. Cir. 2011) 32

SRI Int'l v. Cisco Systems, Inc.,
930 F.3d 1295 (Fed. Cir. 2019) 30

SRI Int'l v. Internet Sec. Sys.,
511 F.3d 1186 (Fed. Cir. 2008) 44

Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.,
655 F.3d 1364 (Fed. Cir. 2011) 31, 37, 53

Streck, Inc. v. Rsch.h & Diagnostic Syss., Inc.,
665 F.3d 1269 (Fed. Cir. 2012) 32

TQ Delta, LLC v. CISCO Systems, Inc.,
942 F.3d 1352 (Fed. Cir. 2019) 50

Trintec Indus. Inc. v. Top-U.S.A. Corp.,
295 F.3d 1292 (Fed. Cir. 2002) 40

Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.,
308 F.3d 1167 (Fed. Cir. 2002) 32, 66

Upjohn v. Mova Pharm.l Corp,
225 F.3d 1306 (Fed. Cir. 2000) 32, 53

Walden v. Georgia-Pacific Corp.,
126 F.3d 506 (3rd Cir. 1997) 59, 64

Washburn & Moen Mfg. v. Beat 'Em All Barbed-Wire,
143 U.S. 275 (1892).....35

Woodland Tr. v. Flowertree Nursery, Inc.,
148 F.3d 1368 (Fed. Cir. 1998) 31, 38

OTHER AUTHORITIES

28 U.S.C. § 1295 2

35 U.S.C. § 102 .....3, 31

35 U.S.C. § 103 3

35 U.S.C. § 271 2

Federal Rules of Civil Procedure Rule 59 2

TABLE OF ABBREVIATIONS

Parties

GSI	Defendant Gilead Sciences, Inc.
GSIUC	Defendant Gilead Sciences Ireland UC
Gilead	Collectively, Defendants Gilead Sciences, Inc. and Gilead Sciences Ireland UC
the Government	Plaintiff United States

Other Entities

CDC	Centers for Disease Control and Prevention
CFC	Court of Federal Claims
district court	U.S. District Court for the District of Delaware
HHS	U.S. Department of Health and Human Services
NIH	National Institutes of Health
PHS	U.S. Public Health Service
PTO	U.S. Patent and Trademark Office
PTAB	Patent Trial and Appeal Board
POSA	Person of ordinary skill in the art

Patents

U.S. Patent No. 9,044,509 B2	the ’509 patent
U.S. Patent No. 9.579,333 B2	the ’333 patent
U.S. Patent No. 9,937,191 B2	the ’191 patent
U.S. Patent No. 10,335,423 B2	the ’423 patent
Patents-in-Suit	Collectively, the ’509 patent, the ’333 patent, ’191 patent, and ’423 patent

Other Terms

IPR	*Inter Partes* Review
JMOL	judgment as a matter of law
MTA	material transfer agreement
PCT	Patent Cooperation Treaty
TDF	Tenofovir disoproxil fumarate
TAF	Tenofovir alafenamide
FTC	Emtricitabine
CROI	Conference on Retroviruses and Opportunistic Infections

I. STATEMENT OF RELATED CASES

Counsel is aware of the following cases pending in this or any other court that may directly affect or will be directly affected by this Court's decision in the pending appeal: *Gilead Sciences, Inc. v. The United States of America*, 20-499C (Fed. Cl.).

II. STATEMENT OF APPELLATE JURISDICTION

The Government brought this patent infringement action under 35 U.S.C. § 271 in the District of Delaware. A jury verdict was rendered on May 9, 2023. After granting a portion of the Government's post-trial motion, the district court entered a judgment of patent invalidity on March 22, 2024. Following Defendants' Rule 59(e) motion, the court entered an amended judgment on May 9, 2024. The Government timely filed its Notice of Appeal on July 5, 2024. This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

III. STATEMENT OF THE ISSUES PRESENTED FOR REVIEW

1. Whether the district court erred by not granting a judgment as a matter of law (JMOL) of no anticipation (under 35 U.S.C. § 102) when the alleged public use and alleged public knowledge lacked legally required corroboration and sufficient evidence of the claims' critical efficacy limitation.

2. Whether the district court erred by not granting a JMOL of nonobviousness (under 35 U.S.C. § 103) or a new trial when (a) none of the primary prior art references teach or suggest the "efficacy" limitation, (b) Gilead relied on nonqualified, noncorroborated background art, and (c) the district court precluded the Government from introducing the PTO's highly relevant evaluation of prior art in IPR proceedings.

3. Whether the district court erred by not granting a new trial given the improper admission of evidence regarding the Government's alleged breach of material transfer agreements.

4. Whether the district court erred by not granting a JMOL of enablement (under 35 U.S.C. § 112) based on insubstantial evidence that "tenofovir prodrug" was not enabled.

IV. INTRODUCTION

Facing a growing AIDS epidemic and the lack of any vaccine to address this public health crisis, a team of Government researchers invented methods of HIV ***pr***e-***e***xposure ***p***rophylaxis (PrEP), which provided the first effective medicinal intervention for the prevention of HIV infections. These inventions have allowed millions of individuals to be protected from HIV infection.

The claimed inventions require administering a combination of antiretroviral compounds ***prior*** to exposure to HIV. Each claim emphasizes the importance of efficacy in preventing HIV by including a "thereby" clause requiring the recipient of the antiretroviral two-drug combination to remain HIV negative. The efficacy of this preventative method distinguishes these claims over the prior art and was not disclosed or suggested in any prior work.

At the time of the Government's inventions, the concept of administering antiretrovirals to otherwise healthy individuals to prevent HIV infection was controversial (in terms of safety, efficacy, cost, and potential risk taking).

In fact, Gilead openly criticized Government efforts to address HIV prevention through PrEP and, even after FDA approval, was reluctant to pursue the use of Truvada for PrEP. Gilead ultimately pivoted from criticizing PrEP to profiting from it. Through its infringement, Gilead has earned billions of dollars in profit, but paid no royalties for using taxpayer-funded innovations.

The Government initiated an infringement action against Gilead in district court. But presented with an array of legally insufficient, misleading, and irrelevant evidence, the jury found no direct infringement. The jury also determined that all claims were anticipated and obvious, and that one claim was not enabled. While granting a JMOL of direct infringement, the district court improperly denied the Government's JMOL motion regarding the invalidity verdicts, which are not supported by substantial evidence, as well as its accompanying motion for a new trial, based on several flawed pretrial rulings.

Specifically, Gilead presented unsupported invalidity theories that lacked the necessary elements of those defenses. Gilead alleged anticipation based on prior public use and prior public knowledge, but did not present substantial evidence of the efficacy required by the "thereby" clause. Additionally, the testimony from Gilead's paid witness regarding alleged public use lacked any independent corroboration. The testimony regarding alleged public knowledge was also uncorroborated, and in particular, there is no evidence the documents Gilead relied upon were ever made public. The jury's anticipation verdict cannot stand.

Regarding obviousness, Gilead failed to present substantial evidence that the prior art taught or suggested the efficacy required by the "thereby" clause. Faced with this deficiency, Gilead's expert witness relied upon the same nonqualified art relied upon for anticipation as evidence of background knowledge held by a

POSA. The district court further erred by precluding the Government from cross-examining Gilead's expert regarding discrepancies between his obviousness conclusions and the findings of nonobviousness reached by the PTAB in denying Gilead's IPR petitions.

The district court also failed to exclude irrelevant, confusing, and prejudicial testimony regarding the Government's alleged breach of material transfer agreements (MTAs), which Gilead improperly used to imply that the Government and its lead inventor behaved unethically and unfairly toward Gilead.

For enablement, Gilead's expert witness presented terse testimony without supporting evidence. The jury's finding on enablement lacks substantial evidence.

This Court should vacate and reverse the district court's denial of a JMOL on anticipation, obviousness, and enablement and remand for a new trial to confirm Gilead's liability for induced infringement and to determine the proper amount of damages.

V. STATEMENT OF THE CASE

A. The Parties.

Plaintiff-Appellant is the United States of America (Government or United States) acting on behalf of HHS. HHS is the owner of the Patents-in-Suit by virtue of its administrative control of CDC. The Patents-in-Suit describe and claim the

first effective medicinal interventions for preventing the acquisition of HIV by uninfected individuals.

Defendants-Appellees are GSI and its wholly-owned subsidiary GSIUC, (collectively, Gilead). Gilead has reaped billions of dollars by manufacturing, distributing, and selling Truvada and Descovy for PrEP throughout the United States. The efficacious use of Truvada and Descovy for PrEP infringes the asserted claims of the Patents-in-Suit.

B. CDC's Groundbreaking Research Led to the Patents-In-Suit.

The inventions at issue relate to methods of HIV pre-exposure prophylaxis[1] (PrEP), which provided the first ***effective*** medicinal intervention for the prevention of HIV infections. The HIV/AIDS epidemic began in the early 1980's and spread globally for decades. HIV prevention research focused on finding an effective vaccine, but those efforts proved fruitless. Roughly twenty years later, in the mid-2000s, a small group of CDC scientists conducted research on the use of oral, multi-drug PrEP for the prevention of HIV and developed the methods claimed in the Patents-in-Suit. APPX02014-02027. Gilead infringes the patented methods by inducing efficacious use of two FDA-approved regimens (Truvada for PrEP and

[1] "Prophylaxis" is also termed "chemoprophylaxis" in this context. APPX02014.

Descovy for PrEP)) for prevention of HIV. These methods are the cornerstone of current efforts to eliminate the virus.

1. Early Single-Drug PrEP Research Showed Limited Efficacy.

While other researchers had previously investigated HIV PrEP regimens, those efforts demonstrated limited efficacy. PrEP research in the mid-1990s was directed entirely to monotherapy with tenofovir (also called PMPA).[2] Most notably, the Tsai study, published in 1995, demonstrated that subcutaneous administration of tenofovir to macaques had the "potential" to prevent an infection from a monkey virus with similarities to HIV. APPX32254-32255; APPX34075-34078. Nonetheless, Tsai's findings were limited because the dosages used were far higher than equivalent human doses. APPX32259-32260; APPX32354. Other studies showed that tenofovir was associated with undesirable loss of bone density and kidney toxicity. APPX32370; APPX33211-33212. Research showed that animals treated over longer periods at Tsai-level tenofovir doses also suffered "pathologic [bone] fractures." *Id.*

[2]Gilead purchased rights to tenofovir, which was invented by Antonin Holy in the Czech Republic. APPX32370–32371.

In the decade after Tsai, PrEP preclinical trials focused on whether tenofovir and its oral pro-drugs, including TDF, [3] might be safely and effectively administered as single-drug PrEP regimens. APPX32255. A CDC preclinical PrEP study led by Dr. Shambavi Subbarao examined the use of oral TDF alone in macaques subjected to repeated rectal viral exposures. APPX37258-37265; APPX32255-32256. The Subbarao study included an improved study design that used (1) a TDF dose that was much lower than Tsai and similar to an anticipated human clinical dose and (2) a "low dose repeated mucosal" model, in which macaques were rectally exposed repeatedly to lower amounts of virus—a manner more akin to human HIV exposure. APPX32182-32183; APPX32386-32387. CDC[4] used this study model to better mimic safe TDF dosing in humans and HIV virus exposure conditions as compared to earlier studies, like Tsai, that simply injected high amounts of drug and virus. *Id*..

The results of the Subbarao study of oral TDF lacked the efficacy seen with Tsai's high-dose injection of tenofovir. APPX32258-32259; APPX32217-32218.

[3] TDF was used in prior art FDA-approved combinations with other drugs to ***treat*** HIV-infected individuals but was not administered to HIV-negative individuals to prevent infection. APPX32734–32736; APPX33325–33326.

[4] The CDC researchers primarily responsible for this model were Drs. Thomas Folks and Ronald Otten, APPX32183, both inventors on the Patents-in-Suit. APPX02014; APPX02028; APPX02042.

While oral TDF delayed infection, all treated macaques ultimately were infected after six or seven weeks of exposures.[5] APPX37258. When the results were presented at a 2004 conference, researchers' reactions were decidedly mixed. APPX32186-32187; APPX32259; APPX37222-37257. While some were encouraged by a "delay in the ability to infect the monkey," many others "looking for a hundred percent success," as had been seen with Tsai, were "very disappointed." APPX32186-32187; APPX32259; APPX32385.

2. The Inventors Identified a Drug Combination to Prevent HIV Infection.

While ongoing human trials of single-drug PrEP using TDF were getting underway, a small group of CDC researchers, including the named inventors Drs. Walid Heneine and Thomas Folks, chose to explore multi-drug PrEP options. By November 2004, this group began conceiving of several two- and three-drug PrEP regimens, evaluating roughly seventeen different drug candidates. APPX32260-32262; APPX34430; APPX34435; APPX39684-39687; APPX32188-32193. Ultimately, the group settled on FTC[6] as the second drug to combine with

[5] These results aligned with a separate TDF-alone study published in 2004. APPX35023–35024; APPX32207–32208.

[6] Gilead purchased rights to FTC, which was invented by Raymond Schinazi at Emory University. APPX32372.

tenofovir or TDF, APPX32261-32262, and efavirenz as a potential third drug (if the two-drug combination was unsuccessful). APPX32262.

The CDC inventors designed their experiments using a repeat low-dose model of sexual transmission with weekly rectal viral challenges for fourteen weeks. APPX32268. This allowed the study to only use eighteen total macaques, while testing roughly 240 exposures in carefully controlled experiments. APPX32268-32270; APPX02018, APPX02025**.** Gilead donated drugs for the study, but did not contribute to its design and was not conducting any PrEP studies. APPX32263-32264.

The CDC inventors confirmed the preventive efficacy of the two-drug regimen through testing. APPX02061-02067; APPX32268-32269; APPX02018. These results demonstrated, for the first time, that it was "possible to have a high level of protection against sexual transmission of HIV" using this two-drug regimen. APPX32268-32270 (discussing APPX02064).

The inventors also investigated the previously unknown PrEP efficacy of FTC, APPX02018, to determine if it would "make sense to combine it with TDF," APPX32264-2265. The inventors demonstrated that FTC (dosed subcutaneously) offered significant protection.[7] APPX32270-32271 (discussing APPX02069).

[7] The completed experiments demonstrated that the regimen had roughly 75 percent efficacy (calculated on a per-exposure basis). APPX32279.

CDC filed a provisional patent application on February 3, 2006 describing its PrEP regimens and the results of the experiments. APPX02057-02082. Shortly thereafter, Dr. Heneine presented the findings at CROI, the "premier HIV conference," where the results were "enthusiastically accepted."[8] APPX32275-32277.

The CDC inventors then tested oral TDF/FTC over a fourteen-week period. APPX32279; APPX02017; APPX02025. The oral TDF/FTC combination regimen showed high efficacy. APPX32279; APPX02025.

CDC then filed a U.S. non-provisional patent application on January 31, 2007. APPX02014.

C. FDA Approved Truvada for PrEP, but Gilead Was Not Interested.

The results from the inventors' research precipitated protocol changes in two ongoing human clinical trials evaluating TDF alone for PrEP but, after the CDC's results, changed to administering Truvada (TDF/FTC)[9] for PrEP. These studies were (1) the iPrEx trial, APPX34343-34355, principally funded by NIH, APPX32383-32386; APPX32389; APPX32441, and (2) the Botswana trial, funded and conducted by CDC, APPX32285-32286.

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[8] CROI accepted CDC's work as a "late breaker" abstract, reserved for "highly impactful data." APPX32276.

[9] Truvada is a pill that contains two drugs: TDF and FTC. APPX34001.

iPrEx was the first trial to generate human clinical data confirming the high efficacy of Truvada for PrEP demonstrated in the inventors' preclinical trials. APPX32389-32390. When the iPrEx results were published, both the CDC researchers and the HIV prevention field "were thrilled" that an effective intervention had finally been shown to work. APPX32390-32394.

iPrEX was one of the principal studies leading to FDA approval in 2012 of Truvada for PrEP as the first medicinal intervention for preventing HIV infections. APPX32393. FDA approved Descovy (TAF/FTC)[10] for PrEP in 2019 as the second such medicinal intervention. APPX33326.

Gilead, however, was reluctant to pursue PrEP. The idea of administering HIV-treatment drugs to otherwise healthy individuals to prevent HIV infection was controversial at the time of CDC's research in the mid-2000s. Tenofovir, TDF, FTC, and other retroviral drugs had known side effects, raising concerns about providing potentially toxic drugs to healthy individuals. APPX32558 ("Because of those toxicities, . . . you got to be careful about the long-term consequences because PrEP . . . is going to go on for a long time."); APPX32615-32616; APPX33222; APPX34324. Gilead also had concerns that PrEP would encourage

[10] Descovy is a pill that contains two drugs: TAF (which is a different tenofovir prodrug than TDF) and FTC. APPX38518.

disinhibition—an increase in risky behavior based on a perceived lower risk of acquiring HIV. APPX34160; APPX32766-32767; APPX33319-33320.

Even after FDA approved a Truvada for PrEP indication in 2012, Gilead remained reluctant to promote it. APPX34159 ("Gilead . . . do[es] not plan to pursue the PrEP indication or to promote its use for PrEP."); APPX32447-32448, APPX32474-32475, APPX32494-32497; APPX32746-32748, APPX32761-32762; APPX37001-37020; APPX32764-32766; APPX40428-40431; APPX33230-33231; APPX32833 (confirming Gilead did not promote Truvada for PrEP from 2012 to late 2015). In 2012, while Gilead was generating more than $3 billion in sales from Truvada for HIV treatment, it did not view PrEP as a commercial opportunity at least because there was "controversy and debate" about whether PrEP "would be used appropriately, . . . lead to [drug] resistance, as well as the further spread of HIV." APPX32820-32821.

D. The Patents-in-Suit All Include an Efficacy Limitation.

The Patents-in-Suit share the same specification and recite methods of preventing HIV infection in humans. The three claims on appeal not only require administering the claimed two-drug combination prior to an exposure to HIV, but also include an efficacy step in which the claimed methods "thereby" result in the inhibition of HIV infection. *See* APPX02027; APPX02041; APPX02055.

The protection provided by the claimed efficacy is disclosed throughout the specification and "necessary to give life, meaning, and vitality" to the claim. APPX10652-10657; APPX02035-02037. During prosecution, the inventors introduced the "thereby" clause to overcome prior art rejections and reflect the claims' unexpected result of preventing HIV infection. APPX08900; APPX08902-08911; APPX38777; APPX38725-38726. The examiner noted the unexpected efficacy of protection when allowing the claims. APPX08985-08986; APPX38777; APPX38725-38726. The PTAB acknowledged that the protection provided by the claimed efficacy "was key in the patent[s'] prosecution," APPX38777, APPX38725, and that "the Specification is filled throughout with references" to efficacious HIV protection, APPX38775, which "is at the heart of the invention." APPX38775, APPX38723.

E. When the Government Sought to License These Patents to Gilead, Gilead Refused and Initiated PTAB Proceedings.

Prior to issuance of the first patent related to the Patents-in-Suit, the '509 patent,[11] NIH officials (who license CDC's patents) reached out to Gilead.

Despite repeated invitations, Gilead refused to take a license to the patents. NIH technology transfer personnel contacted Gilead regarding a potential license

[11] The asserted claim of the '509 patent was determined to lack proper dependency and was held invalid prior to trial, leaving three remaining patents for the jury trial. APPX00032–00033.

at least six times starting in 2014, but received no response. APPX37496; APPX32685-32687; APPX37497; APPX32688-32689; APPX37498-37501; APPX32689-32693. When the NIH technology transfer office finally heard from Gilead in 2017, Gilead claimed it did not need to take a license "because of the [parties'] MTAs (material transfer agreements) and because of the long collaboration between Gilead and the government." APPX32705-32706. Gilead never licensed the Patents-in-Suit.

In contrast, six other pharmaceutical companies licensed CDC's patents in the United States and abroad. APPX37402-37442; APPX32677-32681; APPX37469-37493; APPX37443-37468; APPX39736-39763; APPX39713-39735; APPX39690-396715; APPX32709-32718. All six licensees agreed to a four percent royalty rate on PrEP sales. APPX37419; APPX37487; APPX37462; APPX39755; APPX39729; APPX39706.[12]

In August 2019, Gilead filed four unsuccessful IPR petitions against the original Patents-in-Suit. APPX38863-39317 (cover pages found at APPX38863, APPX38980, APPX39097, APPX39206). The petitions relied upon many references Gilead later presented to the Delaware jury. APPX30503-30507;

[12] Having paid no royalties, Gilead has generated $6.9 billion in sales of Truvada for PrEP since the February 2017 issuance of the '333 patent and $3.1 billion in sales of Descovy for PrEP since receiving FDA approval in October 2019. APPX33268.

APPX30518-30529; APPX30160-30170; APPX30182-30186. The PTAB denied institution in February 2020 because the prior art failed to teach or suggest the efficacy required by the claimed invention. APPX38705-38711; APPX38741-38748; APPX38777-38785; APPX38853-38859. In its unsuccessful petitions, Gilead cited CDC ***post***-exposure prophylaxis (PEP) guidelines as a principal reference for its obviousness arguments. APPX38702-38706; APPX38737-38740; APPX38792-38799; APPX38848-38856. The PTAB found that the guidelines provided no information on PrEP efficacy. APPX38702-38706; APPX38737-38740; APPX38792-38799; APPX38848-38856.

Truvada was one of numerous other HIV treatment drugs that had been recommended as a possible PEP regimen in prior art PEP guidelines. Those recommendations were based upon limited data of what "might work," APPX32251-32252. The recommendations did not indicate that Truvada would work for PEP, much less PrEP, which presents a very different clinical setting. APPX32251-32252; APPX33217; APPX33225-33226.

Unlike PrEP, HIV post-exposure prophylaxis is not subject to human clinical trials, and thus, no PEP regimens have been FDA approved. APPX32251. This is because PEP is generally used in limited situations after a potential HIV exposure, such as accidental needle pricks or sexual exposure to an infected person, which generate insufficient data. APPX32251.

Moreover, PEP is administered ***in an emergency*** to a patient ***after*** a potential exposure to HIV and the patient must take anti-HIV drugs to try to prevent an HIV infection that would require life-long adherence to HIV treatment regimens. APPX33224-33226, APPX38702-38706; APPX38737-38740; APPX38792-38799; APPX38848-38856. By contrast, PrEP involves a ***non-emergency*** decision about whether an individual should take potentially toxic antiretroviral drugs to protect themselves ***before*** a possible future HIV infection.[13] *Id.*

F. Proceedings Below.

On November 6, 2019, the Government filed suit in the District of Delaware, alleging induced infringement by Gilead of the '509, '333, '191, and '423 patents. APPX03001-03076.

Prior to trial, the district court construed the "thereby" clauses, which require an inhibition of HIV infection. The court construed the "thereby" clauses to mean "[t]he human remains negative for the immunodeficiency virus while receiving the administration" and further explained that "[w]hether a host remains negative is based on both a serological and PCR assay if both tests are performed but the

[13] For these reasons, PEP guidelines had no bearing on the PrEP regimen chosen for the human clinical trials. As discussed in Section V.C above, the choice of Truvada for PrEP in clinical trials was driven by CDC's research results.

claims do not require unnecessary testing to be done." APPX31162. The district court determined that the "thereby" clause was the "entirety of the patent" and "necessary to give life, meaning, and vitality to the claim." APPX10652-10657.

1. Pretrial Rulings.

Prior to trial, the district court entertained summary judgment motions and motions *in limine* from both parties, albeit with strict limits.[14]

As set forth in the Government's appeal, three decisions were particularly crucial to the jury trial.

a. The district court denied the Government's motion of no anticipation based on the Conant public use.

First, the Government moved for summary judgment that Gilead's anticipation defense involving Dr. Marcus Conant's alleged public use lacked legally sufficient corroboration. APPX18029-18030. While Dr. Conant claimed to

[14] The parties were limited to three motions *in limine*, with a three-page limit for opening and responsive briefs, and a one-page limit for replies. APPX07211. Summary judgment and *Daubert* motions were limited to fifty pages for opening briefs and twenty-five pages for replies. *Id.* The Government was particularly constricted given that Gilead's expert, Dr. Charles Flexner, submitted a 1,400 page expert report on validity issues, asserting anticipation based on at least eight different references, APPX18671–18839, and obviousness based on seven combinations of ten references, APPX18448–18450, APPX18901–19040. While Gilead agreed to limit its obviousness arguments at trial to three principal references, the Court did not limit Gilead's citation to additional references. APPX31467.

have prescribed Truvada for PrEP prior to the Government's first patent filing, there was no evidence to corroborate that claim.

In opposing the Government's motion, Gilead relied on nine published articles to corroborate Dr. Conant's claim that he prescribed Truvada for PrEP before the February 2006 critical date. APPX24765-24768. However, none of the articles support this claim. APPX25111-25147. Seven were published after the critical date and fail to specify the use of Truvada for PrEP prior to the critical date. APPX25111-25122, APPX25126-25130, APPX25133-25147. Although the other two articles were published prior to the critical date, neither describe Dr. Conant's prescription of Truvada for PrEP. APPX25123-25125 (Viread), APPX25131-25132 (tenofovir).

The district court nevertheless denied the Government's motion and permitted "Dr. Conant's testimony regarding the fact that he was prescribing Truvada for PrEP to at least three patients from 2004 to 2006" because it was "sufficiently corroborated by the articles." APPX00032.[15] The district court did not address that none of Gilead's evidence placed Dr. Conant's Truvada for PrEP prescriptions in the 2004 to 2006 timeframe. *Id.* Instead, it cited Gilead's representations that Dr. Conant would testify that (1) "he prescribed Viread [TDF]

[15] Gilead only relied on two of the nine articles at trial. APPX35856–35859.

up until . . . August of 2004, and then he began prescribing Truvada" upon its FDA approval for ***treatment*** and (2) that he refers to both Viread and Truvada as "tenofovir." *Id.*

b. The district court permitted Gilead to introduce evidence of the material transfer agreements, even though Gilead had notice of the Patents-in-Suit prior to infringement.

Second, the district court denied a portion of the Government's motion *in limine* to exclude evidence of the MTAs as irrelevant and prejudicial. APPX00027 (denying Motion *in limine* No. 1, APPX29272-29276); APPX00027 n.5. While the Government conceded the MTAs might be relevant to "Gilead's subjective belief in the unenforceability of the patents, and thus willful infringement," the Government had already dropped its willfulness claims, as suggested by the district court.[16] APPX29273 (citing APPX29859-29860). Nonetheless, the district court agreed with Gilead that the MTAs were relevant to whether Gilead had the required knowledge of the Patents-in-Suit for induced infringement liability. APPX29278; APPX00027 at n.5.

Dr. Heneine, CDC's lead inventor, negotiated two MTAs with Gilead (APPX34429-34433; APPX34434-34443) to obtain donated drugs for the preclinical studies described in the Patents-in-Suit. APPX32262. The MTAs

[16] The court "suggest[ed]" that the Government "rethink" its willfulness claim "because it's going to bring in an awful lot of bad evidence." APPX28420.

required the PHS, which includes CDC: (1) to "promptly disclose" to Gilead "all results, data, and other information or materials derived from" the donated drugs and (2) "to promptly notify" Gilead "of any Inventions." APPX34431; APPX34436-34437. Gilead agreed that PHS would "retain title to any patent" and would "give serious and reasonable consideration" to a "commercially reasonable" licensing proposal from Gilead. *Id.*

Gilead asserts that it was not promptly notified of CDC's inventions and that it was not aware of any of CDC's patents or applications until 2016. APPX32539; APPX32849. These assertions are belied by the trial record. On August 8, 2007, Gilead received a Derwent alert that identified and described the published nonprovisional application. APPX32523; APPX32529; APPX37819; APPX37862. Likewise, in May 2008, CDC inventor Dr. Robert Janssen identified the published PCT application in a Gilead patent disclosure form he was required to submit upon joining the company. APPX34162-34164; APPX37158-37167; APPX32223-32227; APPX32707-32708.

The same CDC research described in the nonprovisional patent application was also published in a scientific journal in February 2008. APPX37280-37288. The article's cover page included a "competing interests section" that identified the inventors by their initials as being "named in a US Government patent application

related to methods for HIV prophylaxis." APPX37280. Dr. Heneine sent the article to Gilead before publication. APPX32281; APPX37289-37298.

All this evidence was discussed in the Court of Federal Claims (CFC) liability decision on the MTAs—*Gilead Scis., Inc. v. United States*, 163 Fed. Cl. 104, 117-23 (Fed. Cl. 2022)—which was cited in the Government's motion *in limine*. APPX29273-29274. While the CFC did not find this evidence amounted to "notice," it did find that CDC provided notice in a 2014 licensing communication, before the first patent, the '509 patent, issued in 2015.[17] APPX29274; *Gilead Scis*., 163 Fed. Cl. at 120. The district court excluded the CFC decision, but permitted Gilead to "introduce evidence related to the [MTAs] at trial to the extent that it relates to their argument that they did not have knowledge of infringement." APPX00027 n.5. The court provided no other rationale for the MTAs' relevance and barred Gilead from using MTA evidence to argue its "unenforceability defenses." *Id.*

c. The district court excluded evidence of Gilead's failed IPR proceedings and the PTAB's analysis of the PEP Guidelines.

Third, Gilead successfully moved *in limine* to exclude any evidence regarding its failed IPR petitions and proceedings. APPX00027 (granting Motion

[17] By granting summary judgment of invalidity on the asserted claim of the '509 patent, APPX29278–29279, the '333 patent became the earliest remaining patent-in-suit for trial, having issued on February 28, 2017, APPX02014.

in limine No. 1 (APPX29506-29511)). The district court agreed with Gilead that any discussion of Gilead's IPR petitions would be irrelevant and prejudicial, and in turn, "confuse and mislead the jury." APPX29507-29509. The district court rejected the Government's argument that excluding the "IPR proceedings would leave the jury with a misleading impression that the PTO did not consider the prior art Defendants are reraising." APPX29672-29674. In particular, Gilead's expert, Dr. Charles Flexner, admitted at deposition that the PTAB made substantive findings "at odds with his invalidity opinions," APPX29672, including what the prior-art PEP guidelines disclosed, APPX30183-30186 (discussing APPX29528-29529). Dr. Flexner specifically disagreed with the PTAB's findings that PEP guidelines did not provide "any information" regarding PrEP efficacy. APPX30184-30185.

2. Trial Proceedings.

The district court conducted a combined jury and bench trial in May 2023.[18] During the jury trial, Gilead asserted anticipation because "the claimed invention was known by Dr. Robert Grant and/or Dr. Marcus Conant and made available to the public in the United States before the named inventors' date of invention by Dr.

[18] Gilead raised equitable defenses regarding the Government's alleged breach of the MTAs that were tried separately in a bench trial. Those defenses were rendered moot when the jury returned its verdict before a bench ruling. APPX33818.

Robert Grant." APPX31175. Gilead also contended the claimed inventions were made available to the public before the critical date by Dr. John Kaldor, *id.,* and were publicly used by Dr. Conant's patients beginning in 2004. APPX31176.

For obviousness, Gilead relied upon three primary references: (1) ***post***-exposure prophylaxis (PEP) guidelines; (2) the 1995 Tsai publication involving subcutaneous injections of tenofovir alone; and (3) a 2004 Truvada treatment label that did not discuss administration prior to exposure. APPX32978-32987.

For enablement, Gilead presented conclusory testimony from its expert who offered no supporting evidence. APPX32993-32998.

The jury determined that all claims were anticipated and obvious and that claim 18 of the '423 Patent was not enabled. APPX00102. It also returned a finding of no direct infringement. APPX00100-00101.

3. Post-Trial Proceedings.

The government challenged the jury's verdict by moving for JMOL and a new trial. APPX31226-31266.

On direct infringement, the Government moved for JMOL based on unrefuted evidence from the Government's expert, Dr. Robert Murphy, that patients infringed the Patents-in-Suit by using Gilead's Truvada and Descovy products for PrEP in accordance with the claimed methods. APPX31237-31244.

On anticipation, the Government explained that Gilead's public knowledge and public use defenses based on the activities of Drs. Robert Grant, John Kaldor, and Marcus Conant were legally insufficient because there was no disclosure of the efficacy limitation and inadequate corroboration for all three anticipation theories. APPX31244-31252.

On obviousness, the Government pointed to deficiencies in Gilead's proposed prior art combinations, including lack of disclosure of the efficacy limitation. APPX31252-31257. On enablement, the Government explained why Gilead's trial presentation failed to meet its burden of proof. APPX31260-31262.

The Government alternatively moved for a new trial based upon Gilead's presentation of prejudicial evidence to the jury, including Gilead's insinuation that the PTO had not considered the PEP arguments that Gilead presented. The Government was precluded from disclosing that the PTAB rejected Gilead's IPR arguments regarding the PEP guidelines. APPX31258-31260; APPX31263.

In March 2024, the district court decided the JMOL motion and motion for a new trial. APPX00109-00137. It granted JMOL on direct infringement. APPX00109-00118. On the validity issues, the district court denied the Government's JMOL and its request for a new trial. APPX00119-00137.

On anticipation, the court's analysis spanned less than five pages. APPX00119-00123. The district court concluded that the jury verdict of

anticipation was supported by the public knowledge of Dr. Grant. APPX00122-00123. The district court only "briefly touch[ed]" on Dr. Conant's prescriptions to patients and Dr. Kaldor's "prior public knowledge" as alternative grounds. *Id.*

On obviousness, the district court denied the Government's JMOL and relied on the "combination" of Gilead's three references and the evidence of motivation to combine to find a disclosure of the efficacy limitation in the prior art. APPX00127-00128.

For enablement, the district court found that the testimony of Gilead's expert adequately addressed the *Wands* factors and faulted the Government for not cross-examining on this issue. APPX00129-00131.

The district court also evaluated the Government's motion for a new trial based upon its rulings to exclude evidence of Gilead's failed IPR proceedings and to allow evidence regarding the MTAs. The district court denied the motion on grounds that Gilead did not mislead or confuse the jury.

VI. SUMMARY OF THE ARGUMENT

The jury found the asserted claims of the three Patents-in-Suit to be anticipated, obvious, and, regarding claim 18 of the '423 patent, also invalid for lack of enablement. These findings lack substantial evidence, and the district court erred in not granting JMOL in the Government's favor.

Regarding anticipation based on the alleged public use by Dr. Conant, there was no independent corroboration of his paid testimony, which also failed to establish that he even prescribed PrEP, as opposed to PEP. The most contemporaneous evidence, in fact, indicated that he prescribed Viread (TDF-only), not the required two-drug combination.

For the alleged public knowledge by Drs. Grant and Kaldor, there was also a failure to teach the claimed efficacy because the alleged public knowledge related to proposed clinical studies that had not commenced or generated any data. Likewise, there was again a failure to provide necessary corroboration. For Dr. Kaldor's alleged knowledge, Gilead presented no evidence beyond the mere allegations of its expert, Dr. Flexner. For Dr. Grant's proposed study, Gilead relied on two documents that were designated confidential, and for which there was no corroborating evidence they were made public.

Accordingly, there is no substantial evidence of the claimed efficacy limitation (the "thereby" clause), and in turn, no anticipation of the claims by the alleged public use and public knowledge. Further, because of the lack of corroboration, the alleged use and knowledge do not qualify as prior art under section 102.

Regarding obviousness, Gilead similarly failed to establish that its three prior art references taught or suggested the efficacy limitation. The Tsai reference

provided information regarding the efficacy of high doses of tenofovir-alone, not the claimed two-drug combination. The CA PEP guidelines only provided a recommendation on the use of Truvada for PEP,[19] and thus gave no information regarding PrEP efficacy. And the third reference, the 2004 Truvada label, disclosed nothing regarding PrEP or PEP efficacy.

Faced with this deficiency, Dr. Flexner's obviousness testimony improperly relied on the nonqualified art discussed above as evidence of background knowledge of the skilled artisan. In denying JMOL, the district court cited to unsupported testimony that contended generally that PEP efficacy could indicate something about PrEP efficacy. This unsupported testimony does not teach or suggest the "thereby" clause and its required efficacy.

Even if this Court finds substantial evidence of obviousness, a new trial is warranted on that issue because (1) Dr. Flexner's testimony included repeated references to nonqualified prior art and (2) the district court precluded the Government from cross-examining Dr. Flexner on the IPR proceedings, where contrary to his assertions, the PTO concluded that PEP guidelines do not teach or suggest the claimed PrEP efficacy. Likewise, a new trial on all issues is warranted based on the district court's failure to exclude testimony regarding the MTAs

[19] Truvada was one of several recommendations for PEP in the guidelines and was not the preferred regimen. APPX33216–33219.

between Gilead and CDC. Any alleged breaches of those agreements were not relevant to any jury issue and unduly impugned the credibility of Government witnesses.

Finally, regarding the finding of a lack of enablement, Dr. Flexner's incredibly terse testimony on "tenofovir prodrug" in claim 18 of the '423 patent merely stated his position that there were numerous possible prodrug candidates, without any of the required analysis or supporting evidence. That finding also lacks substantial evidence.

VII. ARGUMENT

A. Standard of Review.

This Court reviews JMOL decisions under regional circuit law. The Third Circuit applies a *de novo* standard. *SRI Int'l, Inc. v. Cisco Sys., Inc.*, 930 F.3d 1295, 1308 (Fed. Cir. 2019). A court should grant JMOL "if the record is critically deficient of the minimum quantum of evidence to sustain the verdict" and the appellee fails to satisfy a necessary element of its case. *Acumed LLC v. Advanced Surgical Servs., Inc.*, 561 F.3d 199, 211, 213-14 (3d Cir. 2009) (citation omitted). Such a result does not depend on rejecting the jury's findings on the evidence at trial. *See MobileMedia Ideas, LLC v. Apple, Inc.*, 780 F.3d 1159, 1164 (Fed. Cir. 2015).

JMOL is appropriate if "the jury's findings, presumed or express, are not supported by substantial evidence" or if "the legal conclusions(s) implied [by] the jury's verdict cannot in law be supported by those findings." *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1348 (Fed. Cir. 1998) (alteration in original).

Anticipation by public knowledge under § 102(b) requires clear and convincing evidence of public knowledge of all claim limitations. *See Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1369-70 (Fed. Cir. 2000). "An anticipatory public use under § 102(b) must exhibit all of the claim limitations." *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1337 (Fed. Cir. 2011). Testimony regarding an alleged public knowledge or public use must be corroborated. *See Woodland Tr. v. Flowertree Nursery, Inc*., 148 F.3d 1368, 1371 (Fed. Cir. 1998). Whether oral testimony regarding alleged public knowledge or public use is sufficiently corroborated is a question of fact, which this Court reviews for clear error. *See Fleming v. Escort, Inc.*, 774 F.3d 1371, 1377 (Fed. Cir. 2014).

Obviousness is a legal conclusion that is reviewed *de novo*. *Par Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1194 (Fed. Cir. 2014). The statutory standard is whether the subject matter "would have been obvious at the time the invention was made" to a POSA. 35 U.S.C. §103(a) (pre-AIA). Factual questions underpinning the legal question of obviousness include "(1) the scope and content

of the prior art; (2) differences between the prior art and the claims; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness." *Par Pharm.*, 773 F.3d. at 1193. Denial of a JMOL of nonobviousness is reviewed to determine whether substantial evidence supports the jury's verdict. *See Upjohn Co. v. Mova Pharms. Corp.*, 225 F.3d 1306, 1310 (Fed. Cir. 2000).

Enablement is ultimately a question of law subject to *de novo* review that is based on underlying factual findings that are reviewed to determine whether substantial evidence supports the jury's verdict. *See Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012). For a patent to be enabling, its specification must describe the claimed invention so as to enable a POSA to make and use the invention. *See Amgen Inc. v. Sanofi*, 598 U.S. 594, 612 (2023).

This Court reviews evidentiary rulings under regional circuit law, and the Third Circuit applies an abuse of discretion standard. *Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc*., 637 F.3d 1269, 1284 (Fed. Cir. 2011). This Court applies the same standard for reviewing the denial of a motion for new trial. *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co*., 308 F.3d 1167, 1182 (Fed. Cir. 2002). Under Third Circuit law, a district court should grant a new trial when the jury's verdict is against the great weight of evidence and

either is a miscarriage of justice or cries out to be overturned. *Leonard v. Stemtech Int'l Inc.*, 834 F.3d 376, 386 (3d Cir. 2016).

B. The District Court Erred in Its Anticipation Analysis.

The district court denied the Government's JMOL motion on the issue of anticipation, ruling "[t]he jury was entitled to find" that "testimony in combination with the documents shows that Dr. Grant's and others' prior knowledge met all claim limitations, including the 'thereby' [efficacy] step." APPX00122-00123. That ruling was legally and factually erroneous.

Gilead failed to prove anticipation by clear and convincing evidence. The claimed inventions all require that the method be efficacious in inhibiting an HIV infection when administered prior to an exposure. Gilead, however, presented vague testimony about "expectations" of efficacy. The district court erred by relying on that vague testimony, instead of determining whether the efficacy limitation was disclosed in the references presented at trial—which it was not.

The district court further erred by improperly equating any mention of the use of Truvada "for PrEP" as a disclosure of all steps of the claimed methods. Gilead's hand-waving around "Truvada for PrEP" does not demonstrate clear and convincing evidence of the patented methods, which require efficacy such that the individual remains negative for HIV while receiving the claimed two-drug regimen

The district court also erred in concluding that Gilead sufficiently corroborated the alleged public use and public knowledge. Regarding public use, the court relied on contradictory and inconsistent testimony without any corroborating documents. Also, there was no corroboration that any of the alleged public knowledge was, indeed, public. And one source of alleged public knowledge was wholly uncorroborated.

1. The "Thereby" Clause Requires the Host to Remain Negative Based on Testing.

Each claim includes an efficacy limitation that recites "thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human." APPX02027; APPX02041; APPX02055. The district court construed this limitation to require that "[t]he human remains negative for the immunodeficiency virus while receiving the administration" and explained that "[w]hether a host remains negative is based on both a serological and PCR assay if both tests are performed but the claims do not require unnecessary testing to be done." APPX31162. Gilead had to show by clear and convincing evidence that the prior art disclosed this limitation. *See ATEN Int'l Co. v. Uniclass Tech. Co., Ltd.*, 932 F.3d 1364, 1368 (Fed. Cir. 2019). Because Gilead failed to do so, the district court erred in denying the Government's JMOL of no anticipation.

2. No Purported Public Knowledge or Public Use Meets the "Thereby" Clause.

The district court relied on three sources of alleged public knowledge and use to support the jury's anticipation verdict. APPX00120-00121, APPX00124. None of these disclosed all of the claim limitations and none were properly corroborated by independent evidence.

a. Dr. Conant's purported public use lacked disclosure of all claim elements and was uncorroborated.

The district court improperly credited oral testimony from Dr. Conant, a paid Gilead fact witness,[20] APPX32784, regarding alleged Truvada prescriptions he made for pre-exposure prophylaxis before the invention date. APPX00122-00123. This was the only evidence presented by Gilead of any purported public use of the claimed method by any patient prior to the critical date. The Government moved for summary judgment on Gilead's public use defense because Dr. Conant's alleged prescriptions did not meet all of the claim limitations and his expected testimony was uncorroborated. APPX18029-18030, APPX27488-27490. While the district court acknowledged the need for corroboration, APPX31407-31408, it

[20] "Witnesses whose memories are prodded by the eagerness of interested parties to elicit testimony favorable to themselves are not usually to be depended upon for accurate information." *Washburn & Moen Mfg. v. Beat 'Em All Barbed-Wire*, 143 U.S. 275, 284 (1892).

nevertheless denied the Government's motion, APPX00031-00032. The jury thus received deficient and highly prejudicial testimony that should have been eliminated on summary judgment.

After trial, the Government moved for JMOL of no anticipation on the same grounds as the earlier summary judgment motion because Dr. Conant's testimony (1) did not disclose all claim limitations and (2) was not corroborated and contradicted the documents relied upon by Gilead. The district court improperly denied that motion.

First, there is no evidence that Dr. Conant prescribed efficacious PrEP, even accepting his testimony as true. The district court improperly relied on Dr. Conant's testimony regarding prescriptions to a single patient named "Nick." APPX00122-00123. But there is no evidence that "Nick" received the claimed pharmaceutical combination ***prior to*** exposure to HIV. Dr. Conant testified that, prior to receiving a prescription, Nick was "having sex contemporaneously," APPX32802, and "out there having sex every night," APPX32813. This at best suggests that Dr. Conant prescribed medications to Nick ***after*** he was exposed to HIV from his sexual activities. But such a treatment would have been ***post-*****exposure** ***prophylaxis*** **(PEP)**, which does not anticipate the asserted PrEP claims. APPX33202-33203.

Moreover, Dr. Conant did not testify that Nick's use of Truvada protected him from contracting HIV. APPX32800-32813. Therefore, it could not anticipate several claim elements, including the critical "thereby" clause. Because the district court did not address these issues directly, APPX00122-00123, it erred in concluding that Nick's purported use was clear and convincing evidence "exhibit[ing] all of the claim limitations." *Star Scientific, Inc.*, 655 F.3d at 1337.

Second, the district court erred in finding that Dr. Conant's testimony of purported public use was corroborated. "[C]orroboration preferably comes in the form of physical records that were made contemporaneously with the alleged prior invention." *Juicy Whip, Inc. v. Orange Bang, Inc.*, 292 F.3d 728, 743 (Fed. Cir. 2002). Gilead introduced no physical records corroborating use of the claimed methods by Nick. APPX32792.

Gilead relied on two articles that its counsel described as "imprecise for sure." APPX31409. These August 2006 articles discussing Dr. Conant's activities are not corroborating because they were published ***after*** the February 2006 critical date and do not specify when Dr. Conant began prescribing Truvada (rather than Viread, a tenofovir-only formulation[21]) for PrEP. *See* APPX35856-35859.

[21] Viread contains tenofovir as a single drug. Viread does not contain the combination of tenofovir and emtricitabine required by the claims. APPX37921.

Dr. Conant's alleged prior public use was contradicted by two different articles introduced by the Government. *See* APPX37174-37177, APPX37178-37183. One article, a May 2006 Wall Street Journal article, quotes Dr. Conant as having "prescribed preventative ***Viread*** to five or six patients." APPX35044-35048. Faced with this contradictory article, Dr. Conant guessed that he told the Wall Street Journal that he "was using Tenofovir," rather than Truvada, and speculated that the journal may have "transcribe[d] that as Viread."[22] APPX32806.

Dr. Conant also testified that he provided refills to Nick and that "we tested him every time he came back for a refill." APPX32801. But this testimony was contradicted by a 2007 article where Dr. Conant said that "none [of his patients] ever asked for a refill." APPX37176.

Dr. Conant's trial testimony, provided nearly two decades after the purported events, does not constitute sufficient evidence of public use. Dr. Conant's testimony must be corroborated, *Woodland Tr.*, 148 F.3d at 1371, and Gilead's supposedly corroborating evidence does not survive the rule-of-reason analysis. *Lazare Kaplan Int'l*, 628 F.3d at 1374; *Sandt Tech., Ltd. v. Resco Metal and Plastics Corp.*, 264 F.3d 1340, 1350 (Fed. Cir. 2001).

[22] Even if this Court finds suitable corroboration, Dr. Conant's testimony was not "credible," as is legally required. *See Lazare Kaplan Int'l v. Photoscribe Techs., Inc.*, 628 F.3d 1359, 1374 (Fed. Cir. 2010).

The district court acknowledged the gaps and "inconsistencies within Dr. Conant's testimony," but inexplicably found "that the jury could have reasonably concluded that Dr. Conant's testimony was sufficiently corroborated." APPX00123. Because Gilead's evidence did not corroborate the purported public use, *see Cantrell v. Wallick*, 117 U.S. 689, 696 (1886); *Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1366-69 (Fed. Cir. 1999), the district court's corroboration finding was clearly erroneous as "the record [wa]s critically deficient of the minimum quantum of evidence." *Acumed*, 561 F.3d at 211, 213-214.

The jury should never have heard Dr. Conant's legally insufficient testimony that unfairly prejudiced the jury's evaluation of the validity of the asserted claims.

b. There was no public knowledge of the efficacy step based on Dr. Grant.

i. There was no disclosure of the efficacy step.

The district court denied JMOL on anticipation based on purported public knowledge from Dr. Grant, but did not identify any express disclosure of the efficacy limitation in evaluating that defense. Instead, the district court spent one paragraph referring back to "documents" and citing two pieces of testimony. APPX00121-00122. The district court cited planned future studies and an "expectation" of efficacy, but the claims require more. The claims, as construed, require that the "human remains negative for the immunodeficiency virus while receiving the administration" and "[w]hether a host remains negative is based on

both a serological and PCR assay if both tests are performed but the claims do not require unnecessary testing to be done." APPX31162. No testimony or documents cited by the district court, or presented to the jury, discloses these requirements.

Neither Dr. Grant's testimony about his proposed study nor his former colleague Dr. Kimberly Page's "expectation" for that study, APPX00121-000122, disclose the claimed requirement of thereby inhibiting the establishment of HIV infection in a human. The mere probability or possibility of a claim limitation is insufficient for anticipation. *Trintec Indus. Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002). A proposed study, or a subjective expectation when planning a study, cannot, as a matter of law, prove anticipation of claims that require a result, *id*., particularly because Gilead did not argue the claimed efficacy was inherent. APPX31280 n.9.

The documents cited by the district court in its JMOL opinion are a concept sheet (APPX34173-34176), a rejected study proposal (APPX34177-34290), and meeting minutes (APPX35049-35050), none of which disclose the efficacy limitation. These documents only propose studies, but do not include any results that would meet the claimed efficacy limitation. For example, these documents only:

- Set a goal "to determine" if the "proposed concept" decreases infection risk. APPX34173.

- Indicate the desire "to determine" if the proposed course reduces HIV-1 seroincidence. APPX34192.

Gilead presented ***no evidence*** of any data prior to the critical date disclosing the efficacy of the claimed methods. Dr. Grant confirmed that he "had not tested anyone for HIV" at the time. APPX33204. He also testified that when he submitted his grant application, he "did not know whether even Tenofovir alone would be better than a placebo for HIV prevention," much less the claimed two-drug composition recited in the claimed methods. APPX33204.

Gilead acknowledged that documents cited by the district court "need not serve as anticipatory prior art themselves," APPX31277, yet asserts that they can corroborate public knowledge of the claimed invention. APPX31281. Gilead's position is nonsensical because the cited documents lack the very information needed for corroboration: data demonstrating the efficacy of the claimed method prior to the invention. APPX32906 (explaining APPX34173-34176 as a "concept sheet that was prepared to just - to discuss the rationale for including Truvada"); APPX32910 (explaining that APPX34177-34290 "lays out a blueprint for how the trial ***will be*** conducted") (emphasis added). If the documents do not disclose efficacy, they cannot corroborate public knowledge of the critical efficacy limitation.

Because the evidence does not disclose every claim limitation, the district court erred by denying JMOL of no anticipation. *See AstraZeneca LP v. Apotex, Inc*., 633 F.3d 1042, 1055 (Fed. Cir. 2010) (affirming rejection of anticipation defense where there was no evidence that the claimed once-daily therapy worked for anyone); *Ecolochem*, 227 F. 3d at 1369.

ii. Gilead's expert did not address the efficacy limitation.

There is no other record evidence, much less substantial evidence, supporting the jury's finding of anticipation based on Dr Grant's alleged knowledge, as the documents purporting to show that knowledge did not disclose all limitations of the claimed inventions. And Gilead cannot rely on expert testimony to gap-fill the missing limitation. When asked for the basis for his anticipation opinion, Gilead's expert did not separately address the efficacy limitation, but instead discussed Dr. Grant's proposed study, which had no efficacy data:

> Q: Dr. Flexner, why do you believe the asserted claims are anticipated by Dr. Grant's work?
>
> A: Dr. Grant was **proposing** to use Truvada for HIV prevention in the pre-exposure setting which is the same process claimed in the patents at issue, in August, and December of 2004, at least a year before the government's provisional patent was filed.

APPX32976-32977 (emphasis added). Gilead's expert did not discuss any specific claim limitations in his anticipation analysis. *See* APPX32977.

Gilead's expert acknowledged that the documents supporting purported public knowledge were mere speculative proposals. *See* APPX32974 (draft protocol (APPX34177-34290) "speculates that [Truvada] may prove more effective than Tenofovir alone for chemoprophylaxis or PrEP"); APPX32976 ("study proposals"); APPX32976 (same); APPX32975 (question from counsel as to "the ***possibility*** of Truvada for PrEP for clinical trials") (emphasis added). Absent some showing of inherency—which Gilead failed to present—these documents cannot satisfy Gilead's burden. If mere expectations or proposals could anticipate a patent claim that requires a specific efficacy, then any plan to study a compound would invalidate methods of using that compound. That is not the legal standard for anticipation. *Acumed*, 561 F.3d at 211, 213-214.

iii. The district court erred in ruling that Dr. Grant's documents were public.

Gilead's anticipation theory additionally fails because any allegation of prior public knowledge requires evidence of public accessibility. Not only did Gilead fail to prove that Dr. Grant's concept sheet (APPX34173-34176) or rejected protocol (APPX34177-34290) disclose the efficacy limitation, but also failed to demonstrate that these documents were publicly accessible. Public accessibility requires that a document "has been disseminated or otherwise made available" to a

POSA exercising reasonable diligence. *SRI Int'l v. Internet Sec. Sys.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (citation omitted).

The record lacks substantial evidence of public accessibility of the documents Gilead relied on. The concept sheet is marked as confidential on every page. APPX34173-34176. Dr. Grant marked his materials as confidential because he did not want the information "to spread beyond the very few people who [he] needed" to review it. APPX32439. The only evidence of any distribution was an email attaching the confidential concept sheet to individuals ***within Gilead***. APPX35197. Gilead presented no evidence that the concept sheet was distributed prior to the critical date beyond the single email. Confidential information cannot establish the required public accessibility. *See Cordis Corp. v. Boston Sci. Corp.*, 561 F.3d 1319, 1333-35 (Fed. Cir. 2009).

Dr. Grant's draft protocol, like his concept sheet, was also marked confidential on every page and the only evidence of "distribution" was to three individuals ***within Gilead***. APPX32421-32422. Gilead presented no evidence that the draft protocol was distributed prior to the critical date to any other witness. Dr. Grant testified that "I did not send it broadly and I would not have sent it broadly." APPX32421.

The record lacks substantial evidence that these confidential documents were disseminated or otherwise made available to a POSA exercising reasonable

diligence. The documents were received by individuals within Gilead with an expectation that they would not be distributed further, and Gilead presented no evidence of any further distribution. In *Cordis*, 561 F.3d at 1334-35, this Court affirmed lack of anticipation where a clinician disclosed his work to two commercial entities in an effort to commercialize the technology. Even without an express agreement to keep the document confidential, the record supported an expectation of confidentiality, and there was no evidence that the document was distributed outside of the company.

Like *Cordis*, Gilead presented no evidence that the non-public proposals provided by Dr. Grant were (1) shared by him without any expectation of confidentiality; and (2) publicly distributed prior to the critical date. Instead of proffering evidence that demonstrated public accessibility of the concept sheet or draft protocol, Gilead relied on vague testimony regarding discussions of "Truvada for PrEP" to assert public knowledge of the claimed methods. *See, e.g.*, APPX32923 ("Q: Dr. Page, there is just one thing I would like to ask you about. As of late 2004, was the idea of using Truvada for PrEP a secret? A: No."); *see also* APPX32890; APPX32901-32903, APPX32913-332915, APPX32921-32922; APPX32927-32928, APPX32929-32930.

But generalized testimony about "Truvada for PrEP" is not evidence of the public accessibility of the relevant documents. The only witnesses who testified

about the documents were Dr. Grant and Dr. Page, and they confirmed their confidential nature. Dr. Grant testified that he did not circulate the documents broadly and marked them as confidential. APPX32421, APPX32439. Dr. Page confirmed that the draft protocol was treated confidentially, APPX32921-32922, and that the confidential markings on the concept sheet meant that it was a confidential document, APPX32919-32920. The record lacks substantial evidence of public accessibility of the claimed invention. The district court therefore erred in denying JMOL on lack of anticipation.

c. Uncorroborated testimony of Dr. Kaldor's purported knowledge does not disclose the efficacy limitation.

As alternative grounds for anticipation, the district court cited two pieces of testimony from Gilead's expert about purported knowledge of "Truvada for PrEP" by another clinician, Dr. Kaldor. APPX00123 (citing APPX32975, APPX32991-92). Gilead's unsupported testimony regarding Dr. Kaldor was even more deficient than Dr. Grant's purported public knowledge. APPX32975; APPX32991-32992. Gilead presented no supporting documents, no testimony from Dr. Kaldor, and no discussion of the efficacy limitation. The district court legally erred in ruling that the jury's verdict of anticipation based on Dr. Kaldor's public knowledge could be supported by this facially insufficient evidence. *Acumed,* 561 F.3d at 211, 213-14.

C. The Obviousness Verdict Is Unsupported by Substantial Evidence and Tainted by Nonqualified Prior Art and Improperly Excluded Evidence.

The district court erred by denying the Government's JMOL motion on the issue of obviousness. First, the record lacks evidence that any combination of asserted prior art or asserted background knowledge disclose the "thereby" clause as construed. Without substantial evidence of the claimed efficacy, there is no *prima facie* case of obviousness. Second, even if substantial evidence did exist, Gilead's use of nonqualified art (of alleged public use and public knowledge) throughout Dr. Flexner's analysis on obviousness justifies a new trial. Third, a new trial on obviousness is also justified in light of the district court's exclusion of the IPR proceedings.

1. None of Gilead's Three Prior Art References Teach or Suggest the Claimed Efficacy Provided by the "Thereby" Clause.

While obviousness is a question of law, it turns on several underlying factual findings: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Based on these findings, a party seeking to invalidate a patent must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that

the skilled artisan would have had a reasonable expectation of success from doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

Accordingly, for an obviousness verdict to be supported by substantial evidence, the first inquiry is whether all claim limitations are disclosed in the prior art. *Par Pharm.*, 773 F.3d. at 1194 (citation omitted). If all claim limitations are confirmed to be within the scope of the prior art, only then can the analysis move to the inquiries of whether (i) a motivation to combine and (ii) a reasonable expectation of success exist. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006).

The record here lacks substantial evidence that the combination of any of the three asserted prior art references teaches or suggests the efficacy required by the "thereby" clause as construed. Gilead side-stepped this claim construction and presented only conclusory testimony addressing this essential claimed feature. The district court likewise failed to properly address the scope and content of the prior art with regard to the "thereby" clause and improperly jumped to other parts of the obviousness analysis in an attempt to find substantial evidence.

a. There is no express teaching or suggestion in the primary prior art references of the PrEP efficacy required by the "thereby" clause.

Gilead asserted three prior art references for obviousness: Tsai, APPX34075-34078, the 2004 Truvada label, APPX34001-34027, and the June

2004 California Non-Occupational Guidelines (CA PEP guidelines), APPX34028-34074, and three combinations of these references: (1) Tsai and the 2004 Truvada label[23] *see* APPX32978, (2) CA PEP and the 2004 Truvada label, APPX32983, and (3) a combination of those three references, APPX32987. In Tsai, macaques were administered a monotherapy of tenofovir subcutaneously. APPX34075; APPX32300, APPX32979. The 2004 Truvada label discusses administration of Truvada for HIV treatment, but does not discuss administration for HIV prevention prior to exposure. APPX34001-34027; APPX32985. The CA PEP guidelines discuss various treatments for patients having a potential exposure to HIV. APPX32250, APPX32368-32369, APPX33025-33029.

The district court's finding that these references teach all limitations of the claimed methods, including the efficacy required by the "thereby clause," lacks substantial evidence. None of the cited references teach the "thereby" clause.

Tsai: Dr. Flexner admitted that Tsai does ***not*** teach step (b) of administering a combination of emtricitabine and tenofovir. *See* APPX32979. Because Tsai does not disclose administration of the drug combination, Tsai cannot teach that any host remained negative while receiving that combination. And because Tsai only administered a single drug, tenofovir, and not a combination of drugs as

[23] The 2004 Truvada label does not contain the PrEP indication, which was added in 2012. APPX32556; APPX33325–33326.

required by the asserted claims, Tsai certainly cannot teach that any testing for HIV after administration of the drug combination was based on a serological and PCR assay as required by the "thereby" clause. *See* APPX33214-33215.

Dr. Flexner's conclusory testimony that Tsai meets the "thereby" clause, *see* APPX32979-32980, lacks substantive analysis and fails to address the district court's construction. *See Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1152 (Fed. Cir. 2004). This Court has "repeatedly recognized that conclusory expert testimony is inadequate to support an obviousness determination on substantial evidence review." *TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1359-61 (Fed. Cir. 2019) (collecting cases). That is particularly true here when the conclusory testimony is contradicted by the express disclosure of Tsai, and Dr. Flexner's admission that Tsai does not teach the claimed combination.

2004 Truvada Label: Dr. Flexner never asserted that this reference taught the "thereby" clause. *See* APPX32981. And no other witness made such an assertion. The 2004 label only addresses the use of Truvada for treatment of individuals already infected with HIV, and only in combination with additional HIV treatment drugs. APPX34001-34027.

CA PEP: Dr. Flexner's testimony on the CA PEP guidelines was admittedly terse. *See* APPX32983-32984 ("I promise I will spare you [the details]"). He concluded that CA PEP meets the "thereby" clause, *see*

APPX32984, but thereafter admitted that "CA PEP ***obviously does not teach administration of the drug combination prior to exposure***, it only teaches administration of the combination ***after exposure***." APPX32985 (emphases added). Dr. Flexner also offered no testimony that CA PEP teaches any host remaining negative based on receiving the combination of emtricitabine and tenofovir prior to a potential exposure as required by the "thereby" clause.

In denying JMOL, the district court addressed only the alleged combined teachings of the three references, with only a cursory analysis of the required efficacy of the "thereby" clause. APPX00124. The district court found that "Dr. Flexner testified that Tsai 1995, the August 2004 Truvada Label, and the CA PEP guidelines, when considered in combination, taught each step of the Asserted Claims." *Id.* The district court highlighted that "the jury heard testimony that both Tsai 1995 and CA PEP taught the 'thereby' step and could properly rely on such testimony." APPX00124-00125. The district court gave little weight to the fact that Tsai disclosed only administration of tenofovir alone (and its efficacy for PrEP) and incorrectly concluded that "in combination, Tsai 1995 and the 2004 Truvada® Label, teach administration of both emtricitabine and tenofovir." APPX00125.

For CA PEP, the district court relied on Dr. Flexner's statement that CA PEP provided "'all the teaching necessary' to administer the drug combination for

prevention, prior to a potential exposure"—without any discussion of PrEP efficacy of the claimed two-drug regimen. *Id*. (quoting APPX32985). The district court then pointed to vague testimony from Dr. Flexner that there "are plenty of other examples in infectious diseases of using an anti-infective drug that is known to treat an infectious disease if given before the disease occurs, to prevent that same infection." *Id*. (quoting APPX32952-32954).

The district court similarly relied on unsupported fact witness testimony that addressed the applicability of PrEP generally for HIV prevention in view of PEP efforts—but not the efficacy of the specific claimed regimen. APPX00125; APPX32880 (Smith stating generally that "this [PrEP] approach might work"); APPX32892-32894 (Paxton explaining that PrEP "ma[de] sense" and was a "logical extension from PEP"); APPX32418 (Grant's confidential proposal generally supported by "experience with post-exposure prophylaxis") (quoting APPX34195-34196). The district court never pointed to a specific teaching or suggestion of PrEP efficacy for the claimed two-drug combination.

The district court did even not address its construction of the "thereby" clause or how any of the obviousness references satisfied that construction. APPX00123-00125. Yet during claim construction, the district court acknowledged that protecting an individual from an immunodeficiency retrovirus represented the "entirety of the patent," and thus, the "thereby" clause was

"necessary to give life, meaning, and vitality to the claim." *See* APPX10652-10657.

Because the three references relied upon by Gilead do not teach the "thereby" clause, it was error for the district court to conclude that the combination of these references somehow taught this efficacy limitation based simply on unsupported testimony, most of it not specific to the claimed two-drug regimen. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1294 (Fed. Cir. 2013) (finding nonobviousness where the prior art failed to disclose an efficacy limitation).[24] In *Allergan*, this Court acknowledged the distinctive nature of efficacy limitations and specifically recognized that a prior art disclosure of an administration of specific drugs for a specific purpose does not itself amount to a disclosure of the efficacy of that regimen. *Id*. at 1294.

In this case, the three principal references do not teach administration of the claimed two-drug combination for PrEP, much less the efficacy associated with that regimen. Indeed, it defies logic that the three primary references—alone or in

[24] *See also Star*, 655 F.3d at 1376 (reversing denial of JMOL on obviousness because "[b]oth [prior art references] fail to teach the [recited] claim limitation"); *Upjohn v. Mova Pharm. Corp*, 225 F.3d 1306, 1310-12 (Fed. Cir. 2000); *Beachcombers, Int'l, Inc. v. WildeWood Creative Prods., Inc.*, 31 F.3d 1154, 1162–63 (Fed. Cir. 1994).

combination—teach or suggest the efficacy required by the "thereby" clause when they fail to teach or even suggest the use of Truvada (FTC/TDF) for PrEP.[25]

b. The district court erred in evaluating motivation to combine and reasonable expectation of success.

The district court further erred by relying on trial testimony supporting motivation to combine the asserted prior art and an alleged reasonable expectation of success to bolster its conclusions regarding prior art disclosures of the "thereby" clause. APPX00125-00127. These aspects of an obviousness analysis can only be considered "if all the elements of an invention are found in a combination of prior art references." *Par Pharm.*, 773 F.3d. at 1194. Because there was no disclosure of the "thereby" clause in the prior art, the district court legally erred in finding that evidence of motivation to combine and reasonable expectation of success supported its conclusions about the scope and content of the prior art.

c. There is no teaching or suggestion of the "thereby" clause in the background knowledge and teachings presented at trial.

At trial, Gilead, through Dr. Flexner, repeatedly attempted to bolster the teachings of Tsai, the Truvada label, and the CA PEP guidelines based on alleged

[25] This includes any suggestion that the recommended use of Truvada ***for PEP*** in CA PEP, among numerous recommended regimens, suggests anything about the efficacy of the claimed methods of preventing HIV infection by administering the claimed two-drug regimen to healthy individuals. APPX33025; APPX34044.

evidence of prior public use and public knowledge of Truvada for PrEP. Specifically, Dr. Flexner cited: (1) Dr. Conant's testimony, (2) the confidential Grant documents, and (3) Dr. Kaldor's proposed study. *See, e.g.*, APPX31177 (jury instruction that public knowledge and public use can be considered for obviousness)**.**

Dr. Flexner testified that it would have been "obvious to try" Truvada for PrEP with a "reasonable expectation of success," as Dr. Conant "was already trying it in his patients." APPX32982-32983. Dr. Flexner further noted that this background art demonstrated contemporaneous invention because, "as early as July and August of 2004," Dr. Grant and Dr. Kaldor were already proposing Truvada for PrEP clinical studies, and Dr. Conant had "decided to already go ahead and practice it in his clinical practice." APPX32981-32982. Also, as discussed *infra* Section VII.D.1.a, Dr. Flexner cited the alleged prior public use and public knowledge to undercut the Government's assertions of a long felt but unmet need for the claimed inventions.

But, as explained *supra* Section VII.B.2., there was no public knowledge or use that the claimed methods would be efficacious at preventing HIV invention. Dr. Grant's and Dr. Kaldor's proposed clinical studies included no efficacy data. And even accepting Dr. Conant's uncorroborated testimony as accurate, that testimony showed that Dr. Conant was prescribing to patients already exposed to

HIV, not using methods for pre-exposure prophylaxis. *See supra* Section VII.B.2.a.

No other evidence of knowledge of a POSA appears in the record. When a missing claim limitation "is not evidently and indisputably within the common knowledge of those skilled in the art," any testimony attempting to supply the missing limitation must "be ***supported by evidence and a reasoned explanation***," particularly "where the missing limitation goes to the heart of an invention." *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1363 (Fed. Cir. 2016) (emphasis added); *see also K/S Himpp v. Hear-Wear Techs, LLC*, 751 F.3d 1362, 1365-66 (Fed. Cir. 2014).

While the district court relied on unsupported and vague testimony regarding the general applicability of PEP to the claimed inventions, that testimony provides no evidence suggesting the claimed efficacy of the "thereby" clause in preventing HIV infections. As a result, Gilead never demonstrated that its asserted primary and background prior art taught or suggested the claimed efficacy of the "thereby" clause. Gilead cannot point to anything other than unsupported, nonspecific testimony on this point, which is legally insufficient. *Arendi*, 832 F.3d at 1362-63.

D. A New Trial Is Warranted Based on Gilead's Use of Nonqualified Art and the District Court's Erroneous Evidentiary Rulings.

1. Gilead's Reliance on Nonqualified Prior Art Justifies a New Trial.

To the extent this Court finds that evidence of alleged public use and public knowledge supports Gilead's contentions regarding the content of the prior art and obviousness generally, none of that evidence qualifies as prior art. Accordingly, even if the obviousness verdict is supported by that evidence, a new trial is nonetheless appropriate, as the district court abused its discretion in not granting a new trial. *Leonard*, 834 F.3d at 386.

a. Dr. Flexner relied on nonqualified prior art throughout his obviousness testimony.

As discussed above, Dr. Flexner repeatedly interwove legally deficient evidence of prior public use and public knowledge through his testimony on obviousness. After discussing this evidence as anticipating all asserted claims, Dr. Flexner then testified that it demonstrated the obviousness of the claims based on what those in the art knew and were doing. *See supra* Section VII.C.I.

Dr. Flexner cited this evidence to support his opinions on simultaneous invention, and pointed to Dr. Conant's alleged public use for his opinions on a reasonable expectation of success. *See* APPX32982-32983; APPX32991-32992; APPX33311-33312; APPX33320-33321. He further used the same nonqualified art for his rebuttal to the Government's asserted evidence of objective indicia of

nonobviousness. He challenged the government's evidence of long-felt need with the alleged prior public use and public knowledge, asserting that the "long felt, but unmet need," was met by Drs. Conant and Grant, not the CDC inventors. APPX32991-32992.

More broadly, the jury repeatedly heard that the asserted claims were obvious because the inventions were already publicly disclosed by Drs. Grant and Kaldor, and used successfully in human patients by Dr. Conant. Accordingly, the Government's entire obviousness rebuttal was undercut and prejudiced by Gilead's repeated allegations of public use and public knowledge—as no part of those allegations involved qualified prior art.

b. The prejudice created by the nonqualified art was exacerbated by the jury instructions.

Certain jury instructions further exacerbated the prejudice created by the nonqualified prior art.

First, the district court declined to adopt the Government's proposed jury instruction on obviousness that would have required Gilead to establish prior public knowledge and prior public use *before* those theories could be considered in an obviousness analysis. *Compare* APPX31537-31538 n.27 *with* APPX31177 (Instruction O - "Invalidity - Obviousness"). Because the jury was not so instructed, its analysis was tainted by legally deficient evidence relating to Dr. Conant, the Grant documents, and Dr. Kaldor. *See supra* Section VII.B. Gilead

then leaned into that improper evidence to support its obviousness defense. *See* APPX32971-32975, APPX32983, APPX32986, APPX32991-32992; *see also* APPX31280 n.8, APPX31286, APPX31287 (relying on Dr. Grant).

Second, the district court allowed an instruction that simultaneous invention can provide objective indicia of obviousness. APPX31179 ("When evidence establishes that others contemporaneously conceived of or practiced the claimed invention, that tends to prove that invention would have been obvious."). The Government unsuccessfully objected to this language as reframing the law in a conclusory manner. APPX31543 n.39. Gilead relied on that misleading instruction to support its obviousness arguments. APPX32991-32992. For these reasons, a new trial should be granted on obviousness in view of the prejudicial effect of Gilead's use of nonqualified prior art. *Leonard*, 834 F.3d at 386.

2. A New Trial on Obviousness Is Warranted Based on Excluded Evidence Regarding Gilead's Failed IPR Proceedings.

The jury's evaluation of obviousness was further tainted by the district court's exclusion of all evidence of Gilead's failed IPR proceedings. APPX31457-31458; APPX00027.[26] Aided by that ruling, Gilead made misleading and

[26] The district court did not indicate that its ruling was subject to reconsideration. *See* APPX31458; APPX00027. The Government was therefore not required to reraise its objection. *See Walden v. Georgia-Pacific Corp*., 126 F.3d 506, 519 (3d Cir. 1997).

confusing statements that left the jury with the incorrect impression that the PTO had never considered the use of Truvada for PEP, and PEP guidelines, specifically, in evaluating the nonobviousness of the asserted claims. *See, e.g.,* APPX33314 ("It is my understanding from reviewing the prosecution history of these three patents that the government's patent examiner did not have access to the California PEP June 2004 guidelines."), APPX33382 ("[Y]ou heard the examiner did not consider the California PEP guidelines at all."), APPX33252-33253 ("And you would agree with me that the California PEP guidelines were not considered by the patent examiner before the CDC patents were allowed to issue, correct?"), APPX32134-32135.

It was misleading for Gilead to present this type of testimony and argument to the jury when the PTAB had considered and ***rejected*** Gilead's position that the disclosure of Truvada for PEP in PEP guidelines renders the asserted claims obvious. The PTAB determined that the cited CDC PEP (Jan. 2005) guidelines, APPX34291-34318, did not teach the PrEP efficacy required by the "thereby" clause of the claims. And Dr. Flexner admitted at deposition that the PTAB made substantive findings in denying the IPR petitions that are at odds with his invalidity opinions, including what prior-art PEP guidelines disclosed, APPX30183-6 (discussing APPX29528-29529). Dr. Flexner disagreed with the PTAB's finding

that such guidelines did not provide "any information" regarding PrEP efficacy, APPX30184-30185.

At trial, Dr. Flexner testified that the CA PEP guidelines (APPX34028-34074) teach the claimed efficacy of inhibiting the establishment of HIV. APPX32948. The disclosures relied upon by Dr. Flexner at trial are not materially different from the disclosures of the CDC PEP (Jan. 2005) guidelines considered in the IPR proceedings. Dr. Flexner admitted at trial that both PEP guidelines disclose administration of various antiretroviral medications ***after*** exposure to HIV. APPX32964-32966, APPX32969-32970. The PTAB, however, determined that PEP guidelines cannot teach the "thereby" clause. The PTAB explained that because the CDC PEP (Jan. 2005) guidelines (Smith) "does not describe administering the claimed combination of agents as PrEP [i.e., ***before*** exposure], it does not provide any information about the efficacy of such a combination for PrEP. Thus [the guidelines do] not expressly disclose the limitation of efficacy." APPX38741; APPX38740 (Gilead conceding Smith "expressly teaches post-exposure prophylaxis PEP, not pre-exposure prophylaxis PrEP"); APPX38743; APPX38796. Because of the district court's evidentiary rulings, the Government could not cross-examine Dr. Flexner on this issue, or demonstrate to the jury that Dr. Flexner's opinions on obviousness were inconsistent with the PTAB's findings

that PEP guidelines did not provide any information regarding the efficacy of the claimed inventions.

Given that the disclosures from the PEP guidelines considered in the IPR proceedings are not materially different from the disclosures from the PEP guidelines that were relied upon by Dr. Flexner at trial, the district court's exclusion of the IPR proceedings from the jury trial was prejudicial, and its subsequent refusal to grant a new trial was an abuse of discretion. This Court should order a new trial on obviousness on this basis as well.

E. The District Court Erred in Allowing Irrelevant and Prejudicial Evidence Regarding the Government's Alleged Breach of the MTAs.

The district court also abused its discretion in permitting Gilead to introduce prejudicial evidence regarding the Government's alleged breaches of the MTAs. The Government moved *in limine* to preclude Gilead from presenting these alleged breaches because this evidence would confuse the jury on complicated and irrelevant legal issues as well as unfairly prejudice the Government's case. *See* APPX29272-29276. While the district court expressed concern for juror confusion based on Gilead's presentation of the MTAs, *see* APPX32536-32544; APPX21445-32551, it denied the Government's motion, APPX00027.

As a result, Gilead permeated the record with irrelevant allegations of contractual breaches and purported Government misdeeds in failing to notify Gilead of CDC's patent filings. *See, e.g.*, APPX33391-33392, APPX33397;

APPX32137-32138, APPX32169, APPX32321-32322, APPX32336-32340, APPX32742-32745, APPX32753-32755. Gilead's fact witness, Dr. James Rooney, testified that the Government breached the "prompt notification" provision of the MTAs. *See* APPX32848-32849, APPX32850-32851, APPX32858 ("Q. Did all of the MTAs require the CDC to promptly notify Gilead of any invention? A. Yes. Q. Did the CDC do that? A. No, they did not."). Gilead's counsel also challenged Dr. Heneine's credibility during closing arguments by arguing that he did not "tell anyone about his patent" and he "even kept the patents from his own colleagues at the CDC," APPX33393, and "[i]f Admiral [Jonathan] Mermin didn't know about these patents from somebody in his own division, how could Gilead be expected to know." APPX33394. These assertions had nothing to do with infringement or validity.

Gilead's attack on Dr. Heneine's credibility on this unrelated and complicated legal issue was highly prejudicial. It forced the Government to rebut such allegations because, as the district court acknowledged, they raised issues of credibility of the Government's inventor. See APPX32349, APPX32379. In turn, this became a portion of the court's *post hoc* justification for the evidence to be admissible—a point never raised in its pretrial rulings.[27] APPX00136.

[27] The district court also offered, again for the first time, strained reasoning that the MTAs were also relevant to "why Dr. Conant did not have specific patient

As the district court acknowledged, the only "knowledge" requirement relevant here was whether Gilead had knowledge of the Patents-in-Suit. *See* APPX02098. Gilead readily admitted it had actual knowledge of the patents tried to the jury. *See* APPX32539, APPX32745, APPX32849. Therefore, there was no reason for Gilead to introduce evidence of the MTAs or to complain that it was not "promptly notified" about the patents under those MTAs. The MTA notification provision pertains to an unrelated contractual claim that was not before the jury. Gilead's introduction of the MTA evidence was prejudicial and confusing because Gilead used it to imply that the Government and the CDC scientists had somehow behaved unethically and unfairly.

The district court faulted the Government for not objecting to Gilead's use of the MTAs during trial. APPX00135-00137. The pretrial order, however, explained that this ruling could only be revisited if Gilead introduced evidence "to argue unenforceability defenses before the jury." APPX00027 n.5. Gilead admittedly did not use the MTAs in that manner, APPX31299, and thus the Government did not need to reraise its objections. *See Walden*, 126 F.3d at 517.

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records that would further corroborate his testimony" and "damages (*i.e.*, to show how Gilead's situation was unique from other licensees)." APPX00136.

The district court erred in allowing Gilead to present evidence of the MTAs, and this Court should grant a new trial on all remaining infringement and validity issues on that basis.

F. Gilead Presented Insufficient Evidence that "Tenofovir Prodrug" in Claim 18 of the '423 Patent Is Not Enabled.

The district court's denial of a JMOL of enablement was also legally and factually erroneous. Dr. Flexner's enablement testimony, the only trial evidence Gilead presented on this issue, spans just six transcript pages. *See* APPX32993-32998. He simply gave his "bottom line conclusion" that claim 18 is not enabled because the "tenofovir prodrug" term covers "literally thousands or tens of thousands of possible prodrug candidates." APPX32994-32995. He provided no further explanation and no supporting evidence.

Such testimony is insufficient to prove invalidity by clear and convincing evidence as "some evidentiary support must be offered beyond an expert's conclusory opinion." *Rhone-Poulenc Agro, S.A. v. DeKalb Genetics Corp.*, 272 F.3d 1335, 1358 (Fed. Cir. 2001), *vacated and remanded on other grounds*, 538 U.S. 974 (2003), *and opinion modified and reinstated*, 345 F.3d 1366 (2003). This Court has confirmed that conclusory and speculative expert testimony does not establish that a patent lacks enablement. *See Bruning v. Hirose*, 161 F.3d 681, 686 (Fed. Cir. 1998). In *Bruning*, there was "little, if any, record evidence to support" the party's contention that undue experimentation would have been required, and

this Court explained that "[c]onclusory and speculative testimony by [the party's] expert witnesses will not suffice" to support lack of enablement. *Id.*

Here, Dr. Flexner also provided no record evidence to support his enablement opinion, providing only conclusory and speculative testimony. He testified that the claim cover tens of thousands of possible candidates, some of which he speculated might be ineffective, APPX32994-32997.

Under similar facts, where the defendant's expert provided only "general and vague" statements that "hundreds and hundreds" of ineffective compositions were within the scope of a claim, this Court affirmed the grant of a new trial to overturn a jury verdict of lack of enablement. *Union Carbide*, 308 F.3d at 1186.

In denying JMOL, the district court found that Dr. Flexner's testimony addressed each of the eight *Wands* factors. APPX00130. But that testimony was conclusory, admittedly presented "[u]nfortunately . . . relatively quickly," APPX32995, with less than one minute spent on any given factor, APPX32995-32998, and without any evidentiary support. For example, on the first factor—the quantity of experimentation required to practice the claimed invention—Dr. Flexner simply concluded that "an enormous amount of experimentation" would be required. APPX32995. For the second factor—the amount of guidance presented in the patent—he merely reiterated his unsupported conclusion that the claims cover "tens of thousands of potential prodrugs." APPX32996. His

testimony on the remaining factors was equally conclusory and unsupported. APPX32996-32998.[28]

The district court also cited testimony from the Government's expert witness, Dr. Thakker, as evidence supporting non-enablement. APPX00130-00131. This testimony, however, merely confirms that ***some*** testing is required for the claimed class of prodrugs in view of the disclosures provided by the specification. *Id.* But testimony confirming that ***some*** testing was required cannot prove lack of enablement, which requires "evidence that the amount of experimentation" was "unduly extensive." *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1339-40 (Fed. Cir. 2013).

Dr. Thakker's testimony does not support that conclusion. He testified that a POSA would ***not*** "have to look at tens of thousands of prodrugs," APPX33178, explaining that "you're looking at a very small subset of potential[ly] thousands of molecules." APPX33178-33179. He further explained that there are a finite number of tenofovir prodrugs "that have been tested and evaluated and one can choose from those." APPX33184.

[28] While the district court faulted the Government for not cross-examining Dr. Flexner about enablement, APPX00130, Gilead bore the burden of proof on this defense, APPX31181.

Dr. Thakker's testimony was the only testimony supported by documentary evidence. He explained, for example, that Gilead's Becker reference (APPX39595-395621) teaches how to find and identify additional tenofovir prodrugs that "not only should get absorbed into the bloodstream," but once in the bloodstream would continue to "have stability until it enters the cells which harbor the virus." APPX33176; *see generally* APPX33176-33178. He further explained, based on Gilead's Shaw reference (APPX39589-39594), that "a simple test like a stability toward intestinal homogenate, gives [ ] a good insight" on how tenofovir prodrugs will behave. APPX33174-33175, APPX33179, APPX33179-33180.

Gilead's unsupported and conclusory testimony from Dr. Flexner on enablement does not constitute substantial evidence that claim 18 of the '423 patent lacks enablement. *See Schumer v. Lab. Comput. Sys., Inc*., 308 F.3d 1304, 1315-16 (Fed. Cir. 2002) (finding "generalized testimony as evidence of invalidity is improper"); *see also NexStep, Inc. v. Comcast Cable Commc'ns, LLC*, 119 F.4th 1355, 1374 (Fed. Cir. 2024) (affirming rejection of conclusory expert testimony aptly described as "word salad"). The district court improperly denied the requested JMOL of enablement for claim 18 of the '423 patent, the Government's only asserted claim covering the use of Descovy for PrEP.

VIII. CONCLUSION

This Court should reverse the district court and grant a JMOL of no anticipation, nonobviousness and enablement, as Gilead failed to produce substantial evidence supporting those verdicts. If a judgment of nonobviousness is not entered, the Court should grant a new trial on obviousness based on Gilead's use of nonqualified art and the district court's exclusion of evidence of the IPR proceedings. If any judgment of invalidity is upheld, the Court should alternatively grant a new trial on such issues based on the district court's failure to exclude the MTAs from the jury trial.

December 12, 2024

Respectfully submitted,

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ADDENDUM

ADDENDUM TABLE OF CONTENTS

1.	Order After Pretrial Conference [D.I. 450] ----------	**APPX00025-98**
2.	[REDACTED] Jury Verdict [D.I. 469] ----------	**APPX00099-106**
3.	Judgment Following Jury Verdict [D.I. 471] --------	**APPX00107-108**
4.	Memorandum and Opinion [D.I. 496] ----------	**APPX00109-137**
5.	Order Granting-in-Part Plaintiff's Renewed JMOL and New Trial Motion [D.I. 497] ----------	**APPX00138**
6.	Final Judgment [D.I. 498] ----------	**APPX00139-140**
7.	Order Denying Defendants' Motion to Amend Judgment [D.I. 503] ----------	**APPX00141**
8.	Amended Final Judgment [D.I. 504] ----------	**APPX00142-146**
9.	U.S. Patent No. 9,044,509 [JTX-1] ----------	**APPX02001-2013**
10.	U.S. Patent No. 9,579,333 [JTX-2] ----------	**APPX02014-2027**
11.	U.S. Patent No. 9,937,191 [JTX-3] ----------	**APPX02028-2041**
12.	U.S. Patent No. 10,335,423 [JTX-4] ----------	**APPX02042-2056**
13.	U.S. Patent Provisional Application No. [JTX-9] 60-764,811----------	**APPX02057-2082**

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA,	)	
	)	
Plaintiff/Counterclaim Defendant,	)	
	)	
v.	)	
	)	
GILEAD SCIENCES, INC.,	)	C.A. No. 19-2103 (MN)
	)	
Defendant/Counterclaim Plaintiff,	)	
	)	
and GILEAD SCIENCES IRELAND UC,	)	
	)	
Defendant.	)	

ORDER AFTER PRETRIAL CONFERENCE

At Wilmington, this 28th day of April 2023, after a Pretrial Conference and upon consideration of the: (1) Proposed Pretrial Order (D.I. 433 & 434), (2) parties' motions for summary judgment (D.I. 344, 350 & 362), (3) parties' *Daubert* motions (D.I. 343 & 347) and (4) discussion at the April 24, 2023 Pretrial Conference (D.I. 447), IT IS HEREBY ORDERED that:

1. The Proposed Pretrial Order is ADOPTED as modified by any discussion at the Pretrial Conference. (*See* D.I. 447).

2. A six-day jury trial will begin on May 2, 2023, at 9:00 a.m. with jury selection.[1] Subsequent trial days will begin at 9:00 a.m. Each side should be prepared to present its case to the jury until 4:30 p.m. of each trial day, although the end of the jury trial day may, at the discretion of the Court, be earlier than 4:30 p.m. The bench trial will take place on May 4, May 8 and May

[1] Plaintiff is responsible for providing enough copies of the *voir dire* and a writing utensil for each member of the jury pool, which is estimated to be forty (40) people. Those must be delivered to the Clerk's office by NOON on May 1, 2023.

9, 2023 after the jury is dismissed for the day. Each side should be prepared to present its case to the bench until 6:30 p.m. of each trial day.

3. The trial will be timed. Each side is allowed up to fourteen (14) hours in the jury trial for its opening statement, its direct, cross-examination and redirect, of witnesses, closing arguments and argument of evidentiary issues and any other motions. Each side is allowed up to six (6) hours in the bench trial its opening statement, its direct, cross-examination and redirect, of witnesses, closing arguments and argument of evidentiary issues and any other motions. Each side shall reserve one (1) hour of its fourteen (14) hours for closing arguments before the jury as well as one (1) hour of its six (6) hours for closing arguments before the bench.[2] Time during the trial day that does not neatly fit into one of those categories will be attributed to one side or the other as the Court deems appropriate.

4. There will be thirty minutes to forty-five minutes for lunch and a fifteen-minute break in the morning and in the afternoon each day.

5. Issues that need to be addressed will be taken up at 8:00 a.m. and at the end of the jury trial day or at such other time that the Court determines. Issues – including objections to anticipated exhibits or demonstratives – must be brought to the attention of the Court's Judicial Administrator by 7:00 a.m. on the day on which the evidence objected to will be adduced.

6. For the reasons stated at the Pretrial Conference, 1) Plaintiff's Motion for Partial Summary Judgment (D.I. 350) is DENIED with respect to Sections[3] I and IV and Section II(A)(1)

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[2] As discussed at the Pretrial Conference, the Court will determine whether the parties will give closing arguments for the bench trial either after post-trial briefing is complete or at the close of evidence. (*See* D.I. 447 at 80:1-8).

[3] The section numbers refer to the sections in the respective briefs relating to each motion.

(the Executive Order 10096 issue); 2) Defendants' Cross-Motion for Summary Judgment (D.I. 362) is GRANTED; 3) Defendants' Motion for Summary Judgment (D.I. 344) is DENIED as moot with respect to Sections I and VI, GRANTED-IN-PART with respect to Section VIII (granted as to GSIUC's pre-suit inducement and denied as to GSIUS's post-suit inducement) and DENIED with respect to Sections II, IV, V, VII and IX; 4) Plaintiff's Motion to Exclude Expert Testimony (D.I. 343) is GRANTED-IN-PART with respect to Section II (Mr. Blakeslee's opinions regarding the clinical trial agreements), DENIED as moot with respect to Sections I, IV, V and VI and DENIED-IN-PART with respect Sections III and VII[4]; 5) Defendants' Motion to Exclude Opinions of Dr. DeForest McDuff (D.I. 347) is DENIED as moot with respect to Section II and DENIED with respect to all other issues; 6) Plaintiff's Motion *in Limine* No. 1 (D.I. 434, Ex. 9P.1) is GRANTED-IN-PART with respect to the Court of Federal Claims decision and the clinical trial agreements and DENIED-IN-PART with respect to the material transfer agreements[5]; 7) Plaintiff's Motion *in Limine* No. 2 (D.I. 434, Ex. 9P.2) is DENIED-IN-PART with respect to evidence related to the CDC and FDA encouraging Gilead to seek a PrEP indication; 8) Plaintiff's Motion *in Limine* No. 3 (D.I. 434, Ex. 9P.3) is DENIED; 9) Defendants' Motion *in Limine* No. 1 (D.I. 434, Ex. 9D.1) is GRANTED; 10) Defendants' Motion *in Limine* No. 2 (D.I. 434, Ex. 9D.2)

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4 As noted at the Pretrial Conference, to the extent that Mr. Stoll (Section III) offers opinions on whether Patent Office procedures are more "favorable," whether they would be "successful" or whether evidence is "material," Plaintiff may object at trial. (*See* D.I. 447 at 41:20-42:5). In addition, if Dr. Meyer testifies (Section VII) regarding issue of infringement, Plaintiff may object. (*See* D.I. 447 at 43:20-24).

5 For clarification, Defendants may introduce evidence related to the material transfer agreements at trial to the extent that it relates to their argument that they did not have knowledge of infringement. Defendants, however, may not introduce the evidence to argue their unenforceability defenses before the jury. To the extent that this occurs, Plaintiff may object at trial.

is DENIED[6]; and 11) Defendants' Motion *in Limine* No. 3 (D.I. 434, Ex. 9D.3) is GRANTED-IN-PART with respect to the press releases and DENIED-IN-PART with respect to all other evidence specified.[7] (*See* D.I. 447 at 6:4-73:24).

7. During the Pretrial Conference, the Court reserved ruling on Sections II(A)(2), II(B) and III of Plaintiff's Motion for Summary Judgment (D.I. 350), Section III of Defendants' Motion for Summary Judgment (D.I. 344) and the portion of Plaintiff's Motion *in Limine* No. 2 regarding evidence of federal, state and local agency recommendations on PrEP usage (D.I. 434, Ex. 9P.2). (*See* D.I. 447). The Court considers each of these in turn.

8. First, Plaintiff moves for partial summary judgment on the grounds that Defendants cannot establish their license defense. (*See* D.I. 350 at 19-24). Plaintiff's Motion is GRANTED. Plaintiff argues that the named inventors assigned their rights, title and interest in the Asserted Patents[8] to the Government when they signed a written assignment in 2006 ("the 2006 Assignment").[9] Defendants counter that the 2006 Assignment did not assign rights to the Asserted Patents. Therefore, Defendants argue that when one of the named inventors, Dr. Janssen, licensed

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6 As discussed at the Pretrial Conference, Defendants may re-raise the issues raised by their Motion *in Limine* No. 2 at trial. (*See* D.I. 447 at 68:7-16).

7 As discussed at the Pretrial Conference, if Plaintiff seeks to introduce the press releases for what it believes is a permissible reason, it must raise the issue with the Court before putting the evidence before the jury. (*See* D.I. 447 at 70:9-11). In addition, Defendants may re-raise the arguments presented in its Motion *in Limine* No. 3 if those issues arise at trial. (*See id.* at 72:1-11).

8 U.S. Patent No. 9,044,509 ("the '509 Patent"), U.S. Patent No. 9,579,333 ("the '333 Patent"), U.S. Patent No. 9,937,191 ("the '191 Patent") and U.S. Patent No. 10,335,423 ("the '423 Patent").

9 Plaintiff also argued that rights in the patented inventions vested in the Government under Executive Order 10096 regardless of whether there was a formal assignment. At the Pretrial Conference, the Court denied Plaintiff's Motion with respect to this issue. (*See* D.I. 447 at 6:23-7:20).

his "prior inventions" to Gilead in 2008 via Gilead's Confidential Information and Inventions Agreement ("the CIIA"), this agreement effectively licensed the patented inventions to Gilead. The question before the Court is thus whether the 2006 Assignment transferred rights to the Asserted Patents. The Court holds that it did.

9. In support of its argument, Defendants first contend that "[a]t most, the 2006 Assignment transferred rights to [Provisional Application No. 60/764,811 ("the Provisional Application")]" because the 2006 Assignment contains no language "that assigns rights beyond 'the invention.'" (D.I. 364 at 15). Defendants argue that the Provisional Application lacks written description for the claimed inventions and thus the "invention" named in the Provisional Application cannot be the same as that claimed in the Asserted Patents. (*Id.* at 15 n.11; *see also* D.I. 447 at 10:15-11:18). As Plaintiff points out, however, the language of the 2006 Assignment is broader than Defendants contend. The 2006 Assignment "includes assignment of all Letters Patent that may be granted on the invention . . . and any divisional, renewal, continuation in whole or in part, substitution, conversion, reexamination, reissue, prolongation or extension thereof; and the right to claim priority." (D.I. 350, Ex. 32 at GIL_BLAKESLEE00000162). The 2006 Assignment thus unambiguously assigns rights not only in the "invention" but also in related patents and patent applications, including continuations-in-part, which necessarily include new matter. The Government claimed the Provisional Application as a related application in the Asserted Patents. (*See* '509 Patent, '333 Patent, '191 Patent & '423 Patent). Defendants state that the Asserted Patents only relate to the Provisional Application by a claim of priority but cite only to the language of the 2006 Assignment itself as support. (D.I. 364 at 17 & 17 n.13). Absent any evidence to the contrary, the Court thus finds that the Asserted Patents, which purport to claim priority to the Provisional Application, are related applications such that the 2006 Assignment

assigned rights in the Asserted Patents to the Government. Therefore, Dr. Janssen did not convey rights in the Asserted Patents in 2008 when he signed Gilead's CIIA because he had no rights to convey. Plaintiff is entitled to summary judgment on Gilead's license defense.

10. In addition, Defendants request that the Court look to an assignment signed by the inventors in 2015 ("the 2015 Assignment") to interpret the 2006 Assignment. Defendants argue that the 2015 Assignment (filed with Application No. 11/669,547[10] ("the '547 Application")) contains language that suggests the Government believed the 2006 Assignment did not convey rights to the patented inventions. It is not clear that this is a case in which the Court can look beyond the four corners of the 2006 Assignment given that its language appears to unambiguously assign rights in all related patents (even apparently those that include new matter) and Defendants have failed to show that there is a reasonable interpretation that the Asserted Patents are unrelated. Furthermore, even if the language were ambiguous, it is unclear whether an agreement that post-dates the 2006 Assignment can inform the Court's interpretation of what the parties intended to assign in 2006. *See Dreni v. PrinterOn Am. Corp.,* 486 F. Supp. 3d 712, 727 (S.D.N.Y. 2020) (collecting cases indicating that extrinsic evidence post-dating contract formation should not inform contract interpretation). Regardless, the Court finds that the extrinsic evidence does not change its holding. First, the Government informed the Patent Office that the Government is the assignee of the '547 Application by virtue of the 2006 Assignment in 2014. (D.I. 350, Ex. 45). Second, although the 2015 Assignment contains some language suggesting that the Government was unsure that the 2006 Assignment conveyed rights in the '547 Application, the parties do not dispute that the Government routinely uses these pro forma assignments to ensure complete

[10] The '547 Application issued as the '509 Patent.

assignment of rights. (*See* D.I. 447 at 8:19-9:9 & 13:18-14:1). Therefore, the Court finds that the extrinsic evidence does not change its interpretation of the clear language of the 2006 Assignment.

11. Second, Plaintiff moves for partial summary judgment on the grounds that Defendants cannot show an invalidating prior public use by Dr. Conant. (*See* D.I. 350 at 24-25). Plaintiff's Motion is DENIED. Plaintiff contends that Defendants' argument is only supported by Dr. Conant's uncorroborated testimony that he prescribed Truvada for PrEP to at least three patients between 2004 and 2006. Defendants counter that his testimony is corroborated by several contemporaneous news articles in which he discusses these prescriptions.

12. Uninterested witnesses are subject to the corroboration requirement. *Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1367-68 (Fed. Cir. 1999). "A rule of reason analysis is used to determine the sufficiency of corroboration, under which all pertinent evidence is examined in order to determine whether the inventor's story is credible." *TransWeb, LLC v. 3M Innovative Properties Co.*, 812 F.3d 1295, 1301-02 (Fed. Cir. 2016) (quoting *Sandt Tech., Ltd v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1350 (Fed. Cir. 2001)) (internal quotation marks omitted). This analysis "does not require that every detail of the testimony be independently and conclusively supported by the corroborating evidence." *Id.* (quoting *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1348 (Fed. Cir. 2013)) (internal quotation marks omitted); *see also id.* ("[W]e have repeatedly rejected an element-wise attack on corroboration of oral testimony."). "Circumstantial evidence can be sufficient corroboration." *Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1378 (Fed. Cir. 2018).

13. Plaintiff takes issue with the fact that the news articles that describe Dr. Conant prescribing Truvada for PrEP all post-date the filing date by around six months. The articles that predate the filing date describe Dr. Conant prescribing "tenofovir" for PrEP, which Plaintiff

contends refers to the drug Viread rather than Truvada. Viread contains a prodrug of tenofovir called tenofovir disoproxil fumarate ("TDF"), and Truvada contains both TDF and emtricitabine. (D.I. 447 at 14:13-15-4). At the Pretrial Conference, Defendants stated that Dr. Conant would testify that he refers to both drugs as "tenofovir." (D.I. 447 at 15:24-18:1). In addition, Defendants stated that Dr. Conant will testify that he prescribed Viread up until it was no longer a drug in July or August of 2004, and then he began prescribing Truvada once it was approved. (*Id.*). Based on the totality of the evidence presented in Defendants' briefing and argument at the Pretrial Conference, the Court finds that Dr. Conant's testimony regarding the fact that he was prescribing Truvada for PrEP to at least three patients from 2004 to 2006 is sufficiently corroborated by the articles. The Court reserves on the issue of whether Dr. Conant may testify about further details of these prescriptions (*e.g.*, details regarding specific patients) subject to a proffer of his testimony. The proper scope of his testimony will be determined at trial.

14. Turning to Defendants' Motion for Summary Judgment, Defendants argue that claim 13 of the '509 Patent is invalid for improper dependency.[11] (*See* D.I. 345 at 11-12). Defendants' Motion is GRANTED. Defendants state that claim 13 covers methods in a "primate host," but it depends from claim 12, which covers methods in a "human." ('509 Patent). Defendants contend that, under the Patent's own definition, "primate host" is a broader category than "human," and thus claim 13 fails to properly narrow the scope of claim 12. *See Pfizer, Inc. v. Ranbaxy Lab'ys Ltd.*, 457 F.3d 1284, 1291-92 (Fed. Cir. 2006) ("[A] violation of § 112, ¶ 4 renders a patent invalid."). Plaintiff counters that one could read claim 13 to properly limit claim 12 by interpreting "primate host" in claim 13 as referring to only a human rather than the broader

[11] Defendants' Motion raised the same argument with respect to claim 3 of the '509 Patent. (*See* D.I. 345 at 11). Prior to the Pretrial Conference, the parties informed the Court that claim 3 (along with others) had been dropped. (*See* D.I. 441).

category. (D.I. 367 at 13-14). The claim language, however, states "primate host," not "human." The '509 Patent defines "primate host" as including "a monkey, baboon, chimpanzee, gorilla, and a human." ('509 Patent at 4:18-19). Although there may be circumstances that would allow the Court to correct a possible clerical error in the '509 Patent, Plaintiff failed to request a correction during claim construction, has not requested a correction in its summary judgment briefing and does not argue under the standard for correction. (*See* D.I. 367 at 13-14); *see also Pavo Sols. LLC v. Kingston Tech. Co.*, 35 F.4th 1367, 1373 (Fed. Cir. 2022) (describing the standard for when courts may correct clerical errors). Therefore, the Court will not correct the claim. Claim 13 of the '509 Patent is thus invalid for improper dependency.

15. Finally, in Plaintiff's Motion *in Limine* No. 2 Plaintiff moves to preclude Defendants from offering testimony or argument regarding their theories that they are not liable for inducing infringement based on (1) the CDC and FDA encouraging Gilead to seek a PrEP indication for Truvada and (2) federal, state and local agency recommendations on PrEP usage. (*See* D.I. 434, Ex. 9P.2). With respect to the evidence regarding CDC and FDA encouragement, the Court denied Plaintiff's motion at the Pretrial Conference. (*See* D.I. 447 at 60:4-9). For clarification, Defendants may introduce such evidence at trial to the extent that it relates to their argument that they did not have knowledge of infringement. Defendants, however, may not introduce the evidence to argue their unenforceability defenses before the jury. To the extent this occurs, Plaintiff may object at trial.

16. With respect to the government agency recommendations on PrEP usage, the Motion is GRANTED. Defendants argue this evidence is relevant to show (1) that there is no predicate direct infringement because alleged infringers had an implied license and (2) that Defendants did not intend to cause or actually cause infringement. As to Defendants' implied

license arguments, the only place in the Pretrial Order that implied license is mentioned is under Defendants' acquiescence or estoppel defense which will be tried before the bench. (*See* D.I. 434, Ex. 3P at 12; *see also* D.I. 447 at 62:3-15). Therefore, this evidence is not relevant to any issues presented to the jury regarding direct infringement. As to Defendants' arguments regarding intent and causation, the Court finds that any tangential relevance this evidence may have to inducement is far outweighed by the risk of prejudicing and confusing the jury.

17. As explained at the Pretrial Conference, the parties may not provide witness binders or physical copies of documents (demonstratives, deposition transcripts, etc.) to the Court, but the parties must provide witness binders to the witnesses. The parties shall provide electronic copies of ALL trial exhibits to the Courtroom Deputy and Judicial Administrator by NOON on May 1, 2023. The trial exhibits must be labeled with JTX, DTX or PTX prefixes with exhibit numbers, and the trial exhibits must be organized in a single folder. Additionally, no later than 7:30 a.m. each trial day, the parties shall provide to the Courtroom Deputy and Judicial Administrator electronic copies of witness folders containing the exhibits and demonstratives (if any) to be used on direct examination and cross-examination[12] of any witnesses expected to be called that day.

18. By no later than NOON on April 28, 2023, the parties shall submit a glossary of terms and names to the Court Reporter.

19. Any document that is used for impeachment that is not on the exhibit list will not be admitted into evidence.

20. Any trial logistics should be coordinated through the Courtroom Deputy.

[12] This includes any deposition transcripts or expert reports to be used with witnesses.

Maryellen Noreika

The Honorable Maryellen Noreika
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA, Plaintiff/Counterclaim Defendant, v. GILEAD SCIENCES, INC., Defendant/Counterclaim Plaintiff, and GILEAD SCIENCES IRELAND UC, Defendant.	)	C.A. No. 19-2103 (MN)

VERDICT FORM

Instructions: In answering the following questions and completing this Verdict Form, please follow the directions provided throughout the form and all of the instructions I have given you in the Court's charge. Your answer to each question must be unanimous. Please refer to the Jury Instructions for guidance on the law applicable to each question.

As used herein:

1. **The "'333 patent" refers to U.S. Patent No. 9,579,333.**

2. **The "'191 patent" refers to U.S. Patent No. 9,937,191.**

3. **The "'423 patent" refers to U.S. Patent No. 10,335,423.**

These three patents are together sometimes referred to as the "Asserted Patents."

The "United States" refers to Plaintiff and Counterclaim-Defendant The United States of America. "Gilead" refers to Defendant and Counterclaim-Plaintiff Gilead Sciences, Inc. and Defendant Gilead Sciences Ireland UC collectively. "GSI" refers ***only*** to Gilead Sciences, Inc. "GSIUC" refers ***only*** to Gilead Sciences Ireland UC.

INFRINGEMENT

Truvada® for PrEP

1. **Has the United States proven by a preponderance of the evidence that one or more patients or physicians (either separately or jointly) directly infringed any of the following claims by using Truvada® for PrEP?**

	Yes (finding for The United States)	No (finding for Gilead)
'333 patent, claim 13	_____	X
'191 patent, claim 18	_____	X
'423 patent, claim 18	_____	X

If you answered "NO" for all claims in Question 1, do not answer Question 2 or Question 3, and proceed to Question 4. If you answered "YES" for any claim, answer Questions 2 and 3 for that claim or those claims.

2. **For any claim to which you responded "YES" in Question 1, has the United States proven by a preponderance of the evidence that *GSI* induced infringement of that claim with respect to Truvada® for PrEP?**

	Yes (finding for The United States)	No (finding for GSI)
'333 patent, claim 13	_____	_____
'191 patent, claim 18	_____	_____
'423 patent, claim 18	_____	_____

3. **For any claim to which you responded "YES" in Question 1, has the United States proven by a preponderance of the evidence that *GSIUC* induced infringement of that claim with respect to Truvada® for PrEP?**

	Yes (finding for The United States)	No (finding for GSIUC)
'333 patent, claim 13	_____	_____
'191 patent, claim 18	_____	_____
'423 patent, claim 18	_____	_____

PROCEED TO QUESTION 4

Descovy® for PrEP

4. Has the United States proven by a preponderance of the evidence that one or more patients or physicians (either separately or jointly) directly infringed the following claim by using Descovy® for PrEP?

	Yes (finding for The United States)	No (finding for Gilead)
'423 patent, claim 18	_____	✓

If you answered "NO" in Question 4, do not answer Question 5 or Question 6, and proceed to Question 7. If you answered "YES" in Question 4, answer Questions 5 and 6.

5. Has the United States proven by a preponderance of the evidence that *GSI* induced infringement of claim 18 of the '423 patent with respect to Truvada® for PrEP?

	Yes (finding for The United States)	No (finding for GSI)
'423 patent, claim 18	_____	_____

6. Has the United States proven by a preponderance of the evidence that *GSIUC* induced infringement of claim 18 of the '423 patent with respect to Descovy® for PrEP?

	Yes (finding for The United States)	No (finding for GSIUC)
'423 patent, claim 18	_____	_____

PROCEED TO QUESTION 7.

INVALIDITY

7. Has Gilead proven by clear and convincing evidence that any of the following claims is invalid because it is anticipated?

	Yes (finding for Gilead)	No (finding for The United States)
'333 patent, claim 13	X	
'191 patent, claim 18	X	
'423 patent, claim 18	X	

8. Has Gilead proven by clear and convincing evidence that any of the following claims is invalid because it would have been obvious?

	Yes (finding for Gilead)	No (finding for The United States)
'333 patent, claim 13	X	
'191 patent, claim 18	X	
'423 patent, claim 18	X	

9. Has Gilead proven by clear and convincing evidence that any of the following claims is invalid because it is not enabled?

	Yes (finding for Gilead)	No (finding for The United States)
'423 patent, claim 18	X	

If you answered "Yes" to Question Nos. 2, 3, 5 or 6 (induced patent infringement) for any claim or claims and "No" to Questions Nos. 7, 8 and 9 (invalidity) for that claim or those claims, you must answer Question No. 10. Otherwise, skip to the end of the Verdict Form.

DAMAGES

10. What amount of damages has the United States proven by a preponderance of the evidence it is entitled to recover?

$ _____

PROCEED TO NEXT PAGE.

UNANIMOUS VERDICT

Upon reaching a unanimous verdict on each question above, each juror must sign below, and the foreperson should add the date.

We, the jury, unanimously agree to the answers to the above questions and return them under the instructions of this Court as our verdict in this case.

Foreperson [redacted]

Juror

Juror

Juror

Juror

Juror

May 9, 2023

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA,	)	
	)	
Plaintiff/Counterclaim Defendant,	)	
	)	
v.	)	
	)	
GILEAD SCIENCES, INC.,	)	C.A. No. 19-2103 (MN)
	)	
Defendant/Counterclaim Plaintiff,	)	
	)	
and GILEAD SCIENCES IRELAND UC,	)	
	)	
Defendant.	)	

JUDGMENT FOLLOWING JURY VERDICT

This 15th day of May 2023, the Court having held a jury trial and the jury having rendered a unanimous verdict on May 9, 2023 (*see* D.I. 468, 469), pursuant to Rule 58(b) of the Federal Rules of Civil Procedure, IT IS HEREBY ORDERED that:

1. Judgment is entered in favor of Defendants and against Plaintiff as to direct infringement of the asserted claims[1] for both Truvada® for PrEP and Descovy® for PrEP.

2. Judgment is entered in favor of Defendants and against Plaintiff that all of the asserted claims are invalid on the bases of anticipation and obviousness and that claim 18 of the '423 Patent is also invalid for lack of enablement.

IT IS FURTHER ORDERED that this Judgment shall have the effect of denying as moot all motions made by the parties, either verbally on the record during trial or filed at D.I. 460, 463, pursuant to Rule 50(a) of the Federal Rules of Civil Procedure.

[1] The asserted claims are claim 13 of U.S. Patent No, 9,579,333, claim 18 of U.S. Patent No. 9,937,191, and claim 18 of U.S. Patent No. 10,335,423 ("the '423 Patent").

IT IS STILL FURTHER ORDERED that the deadline for any party to move for costs and attorneys' fees (including under 35 U.S.C. § 285) is extended to fourteen (14) days after the time for appeal has expired or within fourteen (14) days after issuance of the mandate from the appellate court, and no party shall file any such motion before that time.

Maryellen Noreika

The Honorable Maryellen Noreika
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA,	)	
	)	
Plaintiff/Counterclaim Defendant,	)	
	)	
v.	)	
	)	
GILEAD SCIENCES, INC.,	)	C.A. No. 19-2103 (MN)
	)	
Defendant/Counterclaim Plaintiff,	)	
	)	
and GILEAD SCIENCES IRELAND UC,	)	
	)	
Defendant.	)	

MEMORANDUM OPINION

Shamoor Anis, U.S. ATTORNEY'S OFFICE, Wilmington, DE; David C. Weiss, Brian Boynton, Gary L. Hausken, Walter W. Brown, Philip Charles Sternhell, Lena Yueh, U.S. DEPARTMENT OF JUSTICE, Washington, DC – Attorneys for Plaintiff

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March 22, 2024
Wilmington, Delaware

NOREIKA, U.S. DISTRICT JUDGE:

The Court presided over a six-day jury trial from May 2, 2023 to May 9, 2023. (*See* D.I. 450 ¶ 2; *see also* D.I. 476, 477, 478, 479, 480 & 481 ("Tr.")). At the end of the trial, the jury returned a verdict in favor of Defendants Gilead Sciences, Inc. ("GSI") and Gilead Sciences Ireland UC ("GSIUC") (together, "Defendants" or "Gilead") and against Plaintiff the United States ("Plaintiff" or "the United States" or "the government"), finding that there was no direct infringement of the Asserted Claims of three patents owned by the United States, and that all Asserted Claims were invalid on the bases of anticipation and obviousness, and in the case of one asserted claim, also for lack of enablement. Presently before the Court is Plaintiff's renewed motion for judgment as a matter of law or, in the alternative, motion for a new trial (D.I. 487). For the reasons set forth below, the Court will GRANT-IN-PART and DENY-IN-PART Plaintiff's motions.

I. BACKGROUND

This case concerns U.S. Patent Nos. 9,579,333 ("the '333 Patent"), 9,937,191 ("the '191 Patent") and 10,335,423 ("the '423 Patent") (collectively, "the Patents-in-Suit"), all owned by the United States. The Patents-in-Suit relate to two-drug regimens, known as pre-exposure prophylaxis (PrEP), which effectively prevent new HIV infections. Plaintiff filed this action on November 6, 2019, asserting that Defendants induce infringement of claim 13 of the '333 Patent, claim 18 of the '191 Patent, and claim 18 of the '423 Patent (collectively, "the Asserted Claims")[1] by the manufacture, importation, marketing, distribution, labeling, offering for sale, and/or sale of Gilead's Truvada® and Descovy® products when used for PrEP. (*See* D.I. 433 ¶ 1).

[1] Other claims were dropped prior to trial. (*Compare* D.I. 441, *with* D.I. 433). In addition, prior to trial, the Court determined that another claim asserted by Plaintiff, claim 13 of U.S. Patent No. 9,044,509 ("the '509 Patent"), was invalid for improper dependency. (D.I. 450 ¶ 14).

From May 2, 2023 to May 9, 2023, the Court presided over a jury trial. (*See* D.I. 450 ¶ 2; *see also* D.I. 476, 477, 478, 479, 480 & 481). At the end, the jury found that the United States had not proven by a preponderance of the evidence that one or more patients or physicians, either separately or jointly, directly infringed any of the Asserted Claims by using Truvada® for PrEP or Descovy® for PrEP. (D.I. 468 at 2-3; D.I. 469 at 2-3). Because direct infringement is a necessary predicate of induced infringement, the jury did not reach the questions concerning whether either Gilead entity, GSI or GSIUC, had induced infringement with respect to either drug. (*Id.*). The jury further found that Defendants had proven by clear and convincing evidence that all Asserted Claims are invalid as anticipated and obvious, and in addition, that claim 18 of the '423 patent is invalid because it is not enabled. (*Id.* at 4).

On May 15, 2023, the Court entered judgment on the jury verdict under Rule 58(b) of the Federal Rules of Civil Procedure. (D.I. 471). On June 12, 2023, Plaintiff renewed its motion for judgment as a matter of law and included an alternative request for a new trial in that motion. (D.I. 487). Briefing on those motions is complete. (D.I. 489 & 490).

I. LEGAL STANDARDS

A. Judgment as a Matter of Law

Judgment as a matter of law may be entered against a non-moving party if the Court "finds that a reasonable jury would not have a legally sufficient evidentiary basis to find for the party on [an] issue." Fed. R. Civ. P. 50(a)(1). Judgment as a matter of law is appropriate "only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find liability." *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993) (citing *Wittekamp v. Gulf & W. Inc.*, 991 F.2d 1137, 1141 (3d Cir. 1993)). Entry of judgment as a matter of law is a

remedy to be invoked "sparingly." *CGB Occupational Therapy, Inc. v. RHA Health Servs. Inc.*, 357 F.3d 375, 383 (3d Cir. 2004).

Following a jury trial, a renewed motion for judgment as a matter of law under Rule 50(b) may be granted only if the movant demonstrates "that the jury's findings, presumed or express, are not supported by substantial evidence or, if they were, that the legal conclusion(s) implied [by] the jury's verdict cannot in law be supported by those findings." *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1348 (Fed. Cir. 1998) (alteration in original) (quoting *Perkin–Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893 (Fed. Cir. 1984)). Substantial evidence is such relevant evidence that a reasonable mind might accept as adequate to support the finding under review. *See Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018). In determining whether substantial evidence supports the jury verdict, the Court may not make credibility determinations, weigh the evidence, or substitute its own conclusions for those of the jury where the record evidence supports multiple inferences. *See Lightning Lube*, 4 F.3d at 1166. Moreover, in the Third Circuit, when the movant bears the burden of proof on an issue, judgment as a matter of law is appropriate only if "there is insufficient evidence for permitting any different finding." *Fireman's Fund Ins. Co. v. Videfreeze Corp.*, 540 F.2d 1171, 1177 (3d Cir. 1976) (citations omitted); *see also* 9 Wigmore on Evidence § 2495 at 306 (3d ed. 1940).

B. Motion for a New Trial

A new trial may be granted to all or any of the parties and on all or part of the issues in an action in which there has been a trial by jury, for any of the reasons for which new trials have heretofore been granted in actions at law in the courts of the United States. Fed. R. Civ. P. 59(a). Common reasons for granting a new trial are: (1) the jury's verdict is against the clear weight of the evidence and a new trial is necessary to prevent a miscarriage of justice; (2) there exists newly

discovered evidence that would likely alter the outcome of the trial; (3) improper conduct by an attorney or the Court unfairly influenced the verdict; or (4) the jury's verdict was facially inconsistent. *See Ateliers de la Haute-Garonne v. Broetje Automation-USA Inc.*, 85 F. Supp. 3d 768, 775 (D. Del. 2015).

Whether to grant a new trial is a question committed to the Court's discretion. *See Allied Chem. Corp. v. Daiflon, Inc.*, 449 U.S. 33, 36 (1980). Unlike the standard for judgment as a matter of law, the Court need not view the evidence in the light most favorable to the verdict winner when ruling on a motion for a new trial. *See Ateliers*, 85 F. Supp. 3d at 775. "Nevertheless, new trials because the verdict is against the weight of the evidence are proper only when the record shows that the jury's verdict resulted in a miscarriage of justice or where the verdict, on the record, cries out to be overturned or shocks [the] conscience." *Williamson v. Consol. Rail Corp.*, 926 F.2d 1344, 1353 (3d Cir. 1991).

II. DISCUSSION

In its motion for judgment as a matter of law or, in the alternative, motion for a new trial, Plaintiff argues that the Court should upset the jury's findings as to both direct infringement and invalidity. Alternatively, Plaintiff requests a new trial on two grounds, both concerning evidentiary rulings made by the Court pretrial. The Court addresses these issues largely in turn.

A. Plaintiff's Motion for Judgment as a Matter of Law

Plaintiff takes issue with the jury's findings on patent infringement and validity.[2] Concerning direct infringement, Plaintiff argues that it provided unrebutted evidence that at least

[2] At trial and in their post-trial briefing (apart from the question of enablement of claim 18 of the '423 Patent), the parties focused on claim 13 of the '333 Patent as representative or did not differentiate between the asserted claims of the Patents-in Suit. As no party disputes that claims 18 of the '191 and '423 Patents rise and fall with claim 13 of the '333 Patent (*see*, *e.g.*, Tr. 947:17-24), the Court proceeds similarly here.

one patient or physician infringed the Asserted Claims. Regarding invalidity, Plaintiff argues that Defendants failed to meet their burden to prove that the Asserted Claims were anticipated, obvious, and in the case of claim 18 of the '423 Patent, not enabled.

1. Plaintiff's Evidentiary Support for Direct Infringement

The United States relies on testimony from its expert witness on infringement, Dr. Robert Murphy. As relevant here, Dr. Murphy's testimony focused on his personal experience as a physician, including counseling patients and prescribing Truvada® or Descovy® for PrEP, and on his analysis of Risk Evaluation and Mitigation Strategy (REMS) surveys conducted by Gilead, pursuant to FDA request. (*See, e.g.*, Tr. 553:15-554:5, 556:20-557:13, 561:14-562:13, 575:4-587:15). Patent infringement is a question of fact, "reviewed for substantial evidence when tried to a jury." *ACCO Brands, Inc. v. ABA Locks Mfrs. Co., Ltd.*, 501 F.3d 1307, 1311 (Fed. Cir. 2007). A factual finding is supported by substantial evidence if a reasonable jury could have found in favor of the prevailing party in light of the evidence presented at trial. *See Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1357–58 (Fed. Cir. 1999).

a. Dr. Murphy's Personal Experience

The Asserted Claims each include five steps: (1) the preamble, (2) the "selecting" step, (3) the "administering" step, (4) the "thereby" step; and (5) the "wherein" step. (*See* Tr. 567:1-7). Dr. Murphy provided unrebutted evidence of direct infringement based on his personal experience prescribing PrEP and counseling PrEP patients. He testified that he has counseled "many hundreds" of patients on using PrEP and written "dozens" of PrEP prescriptions (Tr. 553:19-554:5) and that PrEP patents and/or physicians practice each step of the Asserted Claims when they follow the Truvada® or Descovy® for PrEP insert instructions. (Tr. 562:3-5, 567:1–590:22).

First, patients using Truvada® or Descovy® for PrEP are periodically tested to confirm they remain HIV negative while receiving the drugs, which confirms that "establishment" of a "self-replicating infection" has been inhibited, as required by the preamble. (Tr. 572:22–574:23; Tr. 578:7–14 (Truvada®); Tr. 600:13–18, 604:2–9 (Descovy®)). Second, the "selecting" step is met where the patient is confirmed as being HIV-negative before beginning PrEP. (Tr. 578:15–579:13 (Truvada®); Tr. 600:13–18, 604:10–23 (Descovy®)). Third, by taking a daily tablet of Truvada® or Descovy®, the "administrating" step of the Asserted Claims is met because the patient is taking a "pharmaceutically effective amount" of the claimed two-drug combination. (Tr. 580:15–581:19 (Truvada®); Tr. 605:14–606:18 (Descovy®)). Fourth, the "thereby" step requires, according to the Court's construction, for the patient to remain "negative for the immunodeficiency virus [e.g., HIV]" while being administered Truvada® or Descovy® for PrEP. (Tr. 583:2–4). The respective inserts both instruct that patients be HIV tested every three months, and patients actually are tested to confirm they remain HIV negative, which infringes the "thereby" step. (Tr. 583:5–22 (Truvada®); Tr. 606:19–607:17 (Descovy®)).

The "wherein" step requires administering the drug combination prior to a potential exposure to HIV, which the Court construed to mean "prior to engaging in activity that could result in an exposure" to HIV. (D.I. 186 at 13). According to Dr. Murphy, his patients did not follow the safe sex practices outlined in the Truvada® and Descovy® inserts, even though he counseled "every one of them" on such practices. (Tr. 590:6–15). Thus, PrEP patients, including his own, were at "high risk" for HIV infection and subject to potential exposures to HIV, as set forth in the Asserted Claims. (*See* Tr. 615:13–616:1, *see also* Tr. 642:6–19 (asserting that "less than one percent" of his patients were not potentially exposed)). For these reasons, Dr. Murphy and his PrEP patients directly infringe the "wherein" step in accordance with the insert instructions

designating PrEP for "high risk" patients and the Court's claim construction. (Tr. 590:16–22; Tr. 583:3–587:4 (Truvada®); Tr. 607:18–609:15, 611:7–25 (Descovy®)).

In response, Gilead focuses on induced, not direct, infringement. Gilead relies on testimony that physicians and patients who follow the instructions on the Truvada® and Descovy® inserts do not infringe because they are not exposed to HIV, by virtue of abiding by the recommended safe sex practices included on the inserts. Although Dr. Murphy acknowledged that patients who strictly follow the safe sex practices in the PrEP labels do not infringe, (Tr. 642:3-11; *see also* D.I. 489 at 19), he noted that based on his own experience, such patients are hypothetical, because "almost none" practice safe sex in reality. (Tr. 590:6-15, 643:2-17). Dr. Charles Flexner, Gilead's expert, confirmed that PrEP patients do not always adhere to safe sex practices, such as correct and consistent condom use. (Tr. 1020:25-1021:7; *see also* D.I. 460 at 3). The evidence may suggest that administration to some patients does not infringe. But that does not undermine the uncontradicted evidence presented that administration to some patients does infringe.

b. Gilead's REMS Survey Data

In addition to his personal experience, Dr. Murphy testified about Gilead's REMS data. The REMS surveys were periodically submitted "assessments" designed to evaluate if "there was compliance" with the label's instructions for safe and effective PrEP usage.[3] (Tr. 458:13-22). Plaintiff argues that Gilead's REMS data demonstrates infringement of all of the Asserted Claims.

[3] The FDA required that Gilead conduct this survey when it applied to for a PrEP designation for Truvada®. (*See* Tr. 455:9-456:6). Although REMS surveys were conducted solely on the use of Truvada for PrEP®, Government witnesses testified that Truvada® data was applicable to the testing rates and behavior of Descovy® for PrEP patients because it involved the "same patient group" or "pool" and the "same clinician group" or "pool." (Tr. 601:17–21, 610:8–14.).

(D.I. 487 at 8). Gilead argues that the jury was entitled to disregard the REMS survey data because of when the surveys were conducted in relation to when the patents were issued and because the surveys presented aggregated data. The Court agrees.

As previously stated, in evaluating a motion for judgment as a matter of law, the Court must view the evidence in the light most favorable to the nonmovant and give it the advantage of every fair and reasonable inference. *Lightning Lube*, 4 F.3d at 1166. Here, Gilead contested that the REMS surveys were evidence of infringement based on the fact that most of the REMS surveys occurred before the date that the earliest asserted patent issued. (D.I. 489 at 20; Tr. 1000:16-20, 1001:8-1003:12, 1012:13-18). Additionally, Gilead's expert, Dr. Flexner, testified that the REMS survey data relied on by the Government fails to show potential exposure to HIV and thus does not include all claim limitations. (*See* Tr. 1000:22-1001:3; D.I. 489 at 22). The jury was entitled to evaluate and believe either or both of these arguments.

c. JMOL Must Be Granted as to Direct Infringement

Because Plaintiff had the burden of proof on the issue of direct infringement, judgment as a matter of law is appropriate only if "there is insufficient evidence for permitting any different finding." *Fireman's Fund Ins. Co.*, 540 F.2d at 1177 (citations omitted). Here, Plaintiff has satisfied that standard in part. Although the Court is not convinced that Plaintiff's reliance on the contested REMS surveys merits relief, Dr. Murphy's essentially unrebutted testimony as to his personal experience does. There is insufficient evidence to support the jury's finding of no direct infringement, and the Court will grant judgment as a matter of law on this issue.

2. Induced Infringement

Under 35 U.S.C. § 271(b), "whoever actively induces infringement of a patent shall be liable as an infringer." Liability for inducing infringement requires "that the alleged infringer's

actions induced infringing acts and that he knew or should have known his actions would induce actual infringements." *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1304 (Fed. Cir. 2006) (en banc) (citing *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 554 (Fed. Cir. 1990)). Inducing infringement thus necessitates "actual intent to cause the acts which constitute the infringement." *Hewlett–Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990). Further, "[t]he requirement that the alleged infringer knew or should have known his actions would induce actual infringement necessarily includes the requirement that he or she knew of the patent." *DSU Med. Corp.*, 471 F.3d at 1304. Intent can be proven by either direct or circumstantial evidence. *See Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1272 (Fed. Cir. 1986).

Because the jury determined that there was no direct infringement, it did not reach the questions concerning whether Gilead induced infringement. Gilead urges that even if the Court were to conclude that the Government is entitled to JMOL of direct infringement, a new trial is not warranted, but instead, the Court should grant JMOL of no induced infringement in favor of Gilead. (D.I. 489 at 23). The Court agrees up to a point; a new trial is not warranted at this juncture, because as described below, the Court will not upset the jury's findings as to invalidity. It will not, however, go further and enter JMOL of no induced infringement for Gilead.

3. Invalidity

Defendants argued that the Asserted Claims are invalid as anticipated, obvious, and in the case of claim 18 of the '423 Patent, not enabled. Specifically, Defendants argued that the Asserted Claims were anticipated by prior public knowledge, relying on three sources: (1) Dr. Robert Grant, (2) Dr. Marcus Conant, and (3) Dr. John Kaldor. Defendants also argued that the Asserted Claims were obvious based on three combinations of references: (1) Tsai 1995 (JTX-12) and the August

2004 Truvada® Label (JTX-10), (2) the 2004 California PEP Guidelines (JTX-11) and the August 2004 Truvada® Label (JTX-10) or (3) all three references together. Lastly, Defendants argued that claim 18 of the '423 Patent was not enabled because a skilled artisan would be unable to practice the claim's full scope without undue experimentation. The jury agreed that the claims are anticipated, obvious, and in the case of claim 18 of the '423 Patent, not enabled. (*See* D.I. 468 at 4; D.I. 469 at 4). The Court finds that substantial evidence supports the jury's verdict on each of the three theories of invalidity.

a. Anticipation

A claimed invention is anticipated when it "was known to or used by others in this country before the date of the patentee's invention." *UCB, Inc. v. Watson Lab'ys Inc.*, 927 F.3d 1272, 1289 (Fed. Cir. 2019) (citation and quotation marks omitted). "A patent is invalid for anticipation under 35 U.S.C. § 102 if a single prior art reference discloses each and every limitation of the claimed invention." *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1351 (Fed. Cir. 2016). A prior art reference demonstrating prior knowledge or use "must have been available to the public." *Woodland Tr. v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370 (Fed. Cir. 1998). "[D]issemination and public accessibility are the keys to the legal determination whether a prior art reference was published," as is statutorily required. *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989) (internal quotation mark and citation omitted). "Anticipation is a factual question, and a jury verdict regarding anticipation is reviewed after trial for substantial evidence." *Eaton Corp. v. Rockwell Int'l Corp.*, 323 F.3d 1332, 1343 (Fed. Cir. 2003). Gilead argues that the Asserted Claims were anticipated by prior public knowledge in 2004 and 2005 for at least three reasons: (1) Dr. Robert Grant proposed a robust clinical trial of Truvada® for PrEP, expected that Truvada® would work effectively, and told many colleagues of his planned study; (2) Dr. Marcus

Conant knew that Truvada® could prevent HIV infection and prescribed it to three of his patients for PrEP; and (3) Dr. John Kaldor approached Gilead to propose using Truvada® for PrEP in a human trial.

i. Dr. Robert Grant

Gilead argues that the jury was entitled to find that Dr. Grant knew of the claimed invention (using Truvada® for PrEP) by at least August 2004, before the earliest alleged invention date (February 3, 2006),[4] and that he communicated that idea to others without restriction. The Government contends that the documents Gilead relies on, a concept sheet (JTX62) and draft protocol (JTX64) to study the use of Truvada® for PrEP, fail to disclose the "thereby" step recited by the claims and were not public, and thus cannot support a finding of anticipation.

Regarding whether these documents were public, the Government focuses on the fact that every page of the documents was marked "confidential" and that the cover page of the protocol included a note that it was "intended only to focus discussions of protocol development among interested parties." (JTX64 at 64.001). The jury, however, heard substantial evidence that the information was not in fact confidential. For example, Dr. Grant testified that he intended his concept sheet to be sent to others, albeit "a very limited audience" (Tr. 407:6-15), and that he sent the document to Gilead, (Tr. 411:16-412:21; *see also* DTX-182 at 1). In addition, Dr. Grant "talked over the idea of adding a [T]ruvada arm" to the clinical trial he was conducting, with Dr. Mary Fanning, who was a project officer at the NIH at the time and later, the NIH's associate director of clinical research, "who seemed to be very enthusiastic about the idea." (DTX-182 at 1; *see also* Tr. 412:14-413:19). Dr. Grant also shared his draft protocol with "three people at

[4] Viewing the evidence most favorably to Gilead, *see Lightning Lube*, 4 F.3d at 1166, the earliest date of invention is February 3, 2006, which is the filing date of the provisional application for the '509 Patent.

Gilead" (Tr. 421:13-422:4) and discussed using Truvada® for PrEP with the Gates Foundation to secure more funding (DTX-155 at 2).

The jury also heard from other witnesses who confirmed public knowledge of Truvada® for PrEP before the invention date. Dr. Fanning testified that Dr. Ward Cates and Family Health International knew that Dr. Grant wanted to give Truvada® for PrEP to humans by March 2005 because "Bob Grant would talk to everybody." (Tr. 890:10-20). Dr. Page, Dr. Grant's co-investigator on the Peru PrEP trial, recounted many conversations in 2004 in which she and Dr. Grant discussed Truvada® for PrEP. (Tr. 901:12-903:19, 913:14-915:14, 921:1-922:2). She confirmed that by late 2004, Truvada® for PrEP was not a secret. (Tr. 923:2-5). Similarly, Dr. Thomas Coates, co-director of the HIV Prevention Trials Network, testified that "Truvada for PrEP was being discussed" as soon as the FDA approved Truvada® for HIV treatment in August 2004, and that the use of Truvada® for PrEP was "a common topic of discussion" within this group's "entire network of scientists." (Tr. 927:11-928:15). Dr. Coates also recalled discussing Truvada® for PrEP with NIH and CDC personnel in 2004. (Tr. 929:7-930:14). Dr. Grant and his team had discussed adding Truvada® to PrEP trials with Dr. Coates as well as Dr. Cates and Dr. Kenneth Mayer by January 12, 2005, all of whom were "interested in [adding] a Truvada arm for their prevention studies." (DTX-155 at 2; *see* Tr. 913:14-915:8). The jury heard and evaluated the competing evidence and was free to decide that Dr. Grant's knowledge was public despite the "confidential" marking on the concept sheet and protocol. The Court will not reweigh that evidence.

Similarly, the Government's contention that the documents do not disclose the "thereby" step of the Asserted Claims fails. The jury heard testimony that Dr. Grant was prepared "to enroll 2,700 humans in [his] proposed study" of Truvada® for PrEP (Tr. 410:2-5). Dr. Page confirmed

the research team's confidence in Truvada® for PrEP, testifying that she had a "very high expectation" that it would work because "[t]here was a good body of literature to support" that it would and because it was known that "two drugs were better than one." (Tr. 916:10-15). The jury was entitled to find that this testimony in combination with the documents shows that Dr. Grant's and others' prior knowledge met all claim limitations, including the "thereby" step.

ii. Dr. Marcus Conant and Dr. John Kaldor

Having already determined that the jury's anticipation verdict is supported by substantial evidence, the Court will only briefly touch on the alternative grounds for support put forth by Gilead. First, Gilead argues that the jury's anticipation verdict is reinforced by Dr. Conant's prescriptions to at least three patients who used Truvada® for PrEP before the invention date. The Government does not dispute that the jury could have found Dr. Conant credible, but instead argues a lack of corroboration for his testimony. Whether testimony is sufficiently corroborated is a question of fact. *TransWeb, LLC v. 3M Innovative Props. Co.*, 812 F.3d 1295, 1302 (Fed. Cir. 2016). There are no hard and fast rules as to what constitutes sufficient corroboration, and each case must be decided on its own facts. The law has "repeatedly rejected an element-wise attack on corroboration" by not requiring that every claim limitation be included in each piece of corroborating evidence or "that every detail of the testimony be independently and conclusively supported." *Id.* at 1301-02 (citations omitted); (*see also* D.I. 450 ¶ 12).

Here, the jury saw contemporaneous evidence corroborating Dr. Conant's account, including articles from 2006 quoting Dr. Conant as having prescribed Truvada® for PrEP to three of his patients, a practice that he testified he began right after Truvada® was approved in 2004. (*See* DTX-509 at 2; DTX-510 at 2; Tr. 793:22-796:11). The Government introduced other articles quoting Dr. Conant as prescribing tenofovir or Viread® for PrEP to many patients (*see* DTX-126;

PTX-213), which Dr. Conant testified that he did until the FDA approved Truvada®, at which point he switched to the "better combination of drugs," namely Truvada®. (Tr. 790:23-792:2). The jury also heard specific details about Dr. Conant's patient, Nick, whom Dr. Conant prescribed Truvada® for PrEP, not PEP, which he confirmed while testifying. (Tr. 800:17-803:5). Although it may be that there were a few inconsistencies within Dr. Conant's testimony and between it and the documentary evidence Gilead presented, the Court finds that the jury could have reasonably concluded that Dr. Conant's testimony was sufficiently corroborated in order to support its finding of anticipation.

As to prior public knowledge of Dr. Kaldor, Dr. Flexner testified that Dr. Kaldor knew of Truvada® for PrEP and wanted to use it in a study in 2005. (Tr. 975:3-12, 991:20-992:9). He further testified that Dr. Kaldor approached Gilead in the United States asking for Truvada® for use in a human trial he was proposing. (*Id.*). The Government did not cross-examine Dr. Flexner on this testimony, nor did it object to the jury instruction on Dr. Kaldor. (*See* D.I. 464 at 20).

The Court finds that each of these sources of prior public knowledge and use provides substantial evidence of anticipation supporting the jury's verdict.

b. Obviousness

Turning now to obviousness, Plaintiff maintains that Gilead has not proven that the Asserted Claims are obvious. Although obviousness is ultimately a question of law, it is based on underlying factual findings. *See Game & Tech. Co. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1379 (Fed. Cir. 2019). "What a reference teaches and whether a person of ordinary skill in the art would have been motivated to combine the teachings of separate references are questions of fact." *Pregis Corp. v. Kappos*, 700 F.3d 1348, 1353 (Fed. Cir. 2012). "Where, as here, the jury made no explicit factual findings regarding obviousness, [the Court] must determine whether the implicit

findings necessary to support the verdict are supported by substantial evidence." *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1294 (Fed. Cir. 2009) (citing *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1310 (Fed. Cir. 2000)). Specifically, a jury's "verdict of obviousness must be supported by facts of (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) any objective indicia such as commercial success or long-felt need." *Id*.

Defendant offered three combinations of references to show that the Asserted Claims were obvious to a person of ordinary skill in the art. Having found that the jury's verdict of invalidity based on anticipation is supported by multiple grounds, the Court addresses just one ground of obviousness here and finds that substantial evidence supports the jury's verdict.

i. Tsai 1995, the August 2004 Truvada Label, and CA PEP Guidelines

Dr. Flexner testified that Tsai 1995, the August 2004 Truvada® Label, and the CA PEP Guidelines, when considered in combination, taught each step of the Asserted Claims. (Tr. 987:6-17). According to Dr. Flexner, both Tsai 1995 and CA PEP teach: (1) the preamble (Tr. 978:20-979:1, 984:6-9), (2) the "selecting" step (Tr. 979:2-8, 984:9-12), (3) half (in the case of Tsai) or all (in the case of CA PEP) of the "administering" step (Tr. 979:9-14, 984:12-20), and (4) the "thereby" step (Tr. 979:15-980:1, 984:21-25). Dr. Flexner further testified that Tsai teaches (5) the "wherein" step (Tr. 980:2-13). The 2004 Truvada® Label, in combination with Tsai and CA PEP, also teaches the "administering" step. (Tr. 981:5-9, 985:6-11).

The focus of the Government's argument is that none of the references teach the "thereby step." According to the Government, Tsai does not teach the "thereby" step because it refers only to the inhibition of a self-replicating infection in *monkeys*, not in humans, as required by the Court's construction of this step. The jury however, heard testimony that both Tsai 1995 and CA

PEP taught the "thereby" step and could properly rely on such testimony. Dr. Flexner testified that because "Tsai was presenting this monkey model as a model for human infection with HIV," the steps Tsai teaches, including the "thereby" step, are applicable to humans. (Tr. 980:14-981:2). He further noted that "[t]here are some things that we can ethically do in monkeys, that we cannot ethically do in humans," specifically including "conduct[ing] experiments where we challenge humans with HIV." (Tr. 980:18-21). Further, several witnesses confirmed the significance of Tsai's disclosure that tenofovir provided complete protection from HIV infection. (Tr. 796:20-797:8 (Dr. Conant), Tr. 955:14-956:21 (Dr. Flexner), Tr. 1088:4-1089:17 (Dr. Johnson); *see also* Tr. 733:5-734:1 (Mr. Alton), Tr. 870:2-871:2 (Dr. Dieffenbach), Tr. 201:15-203:19 (Dr. Folks), Tr. 419:3-420:1 (Dr. Grant), Tr. 295:9-296:17 (Dr. Heneine)).

The Government also argues that Tsai does not disclose the "administering" step because only one drug was used in the study, not the two required by the claim language. The jury heard testimony however, that in combination, Tsai 1995 and the 2004 Truvada® Label, teach administration of both emtricitabine and tenofovir. (Tr. 981:3-14). In addition, a named inventor and Government witness, Dr. Walid Heneine, acknowledged that Tsai 1995 taught that tenofovir could be combined with another compound to prevent HIV. (Tr. 298:24-299:18). Gilead's expert, Dr. Flexner, further testified that a physician or clinician would have been highly motivated to combine Tsai with the "safety, efficacy, tolerability, and the favorable resistance profile" of tenofovir and emtricitabine in an oral combination, as taught by the 2004 Truvada® Label. (Tr. 981:3-982:7).

Regarding the "wherein" step, neither CA PEP nor the 2004 Truvada® Label describe administration "prior to exposure." Gilead acknowledges this and argues, based on Dr. Flexner's testimony, that the efficacy of Truvada®, as explained by the 2004 Truvada® Label, combined

with CA PEP would provide a person of ordinary skill in the art with "all the teaching necessary" to administer the drug combination for prevention, prior to a potential exposure. (Tr. 985:1-15). Indeed, the jury heard that there "are plenty of other examples in infectious diseases of using an anti-infective drug that is known to treat an infectious disease if given before the disease occurs, to prevent that same infection." (Tr. 952:2-954:6). Dr. Lynn Paxton explained that PrEP "ma[de] sense," and was a "logical extension from PEP," and that doctors "had been doing postexposure prophylaxis for HIV for many years." (Tr. 892:24-894:17). Other witnesses agreed that efficacy for PEP showed efficacy for PrEP. (*See, e.g.*, Tr. 416:25-418:16 (Grant agreeing with a statement he wrote in 2004 that "evidence supporting the efficacy of prophylaxis with and [sic] antiretroviral and decreasing HIV conversion derives primarily from the experience with post-exposure prophylaxis"), Tr. 879:19-881:15 (Smith stating that "if you can . . . stop [HIV infection] after exposure, then you should be able to stop it before exposure.")). Moreover, Tsai teaches this step because "15 of the 25 animals in the Tsai 1995 experiment received Tenofovir four hours before exposure to the immunodeficiency retrovirus." (Tr. 980:2-13).

The jury also heard testimony that motivation to combine existed for the combination of Tsai and the 2004 Truvada Label, CA PEP Guidelines and the 2004 Truvada® Label, and all three references together. Dr. Flexner testified that:

> for people who wanted to prevent this infection in individuals at risk, the only tool we had in our tool box at that time was a drug or a drug combination. And knowing what was known then in August 2004 about the efficacy of Tenofovir in animal models, and the availability of an effective, safe, well tolerated once a day oral drug combination, in this case, Truvada, I think a person of skill in the art would have seen that as the best tool we had to prevent HIV in humans.

(Tr. 981:22-982:7 (further testifying that Truvada was an "obvious tool")). Dr. Flexner also testified that the CA PEP Guidelines recommended the use of Truvada® for HIV prevention in

humans in the PEP setting, and that Truvada® was known to be safe, effective, tolerable, and convenient for patients in the treatment context. (Tr. 985:16-986:2). Finally, Dr. Flexner testified that a skilled artisan "would have had motivation to put [all three references] together." (Tr. 987:6-17). The jury also heard testimony that a person of ordinary skill in the art would have had a reasonable expectation of success based on these combinations of references. (Tr. 982:12-983:3, 986:3-16; *see also* Tr. 953:11-954:6 & 881:7-15 (Doctors knew of "plenty of other examples" of using treatment drugs to prevent infection, and that PrEP should work just like PEP)).

Based on the combination of the three references discussed above and relatedly, the motivation to combine, the jury reasonably could have found that Defendants met their burden to prove invalidity due to obviousness by clear and convincing evidence. Thus, the verdict as to obviousness will remain undisturbed.

ii. Secondary Considerations

The United States devotes little space in its briefing to address secondary considerations, relying on its argument that the prior art references do not contain all elements of the Asserted Claims, and they therefore do not establish a *prima facie* case of obviousness. (D.I. 490 at 13). Because the Court finds that the jury's verdict as to obviousness was supported by substantial evidence, it must consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). It addresses those here.

The jury was entitled to credit Gilead's expert (Dr. Flexner) over the Government's (Dr. Grant) in finding that secondary considerations do not overcome the obviousness of the Asserted Claims. Beginning with unexpected superior results, Dr. Flexner explained that the

closest prior art included Tsai 1995, which showed 100% protection, while the Government's monkey study using Truvada® showed only 50% (or, according to the Government, 66.6%) efficacy. (Tr. 987:23-988:20, 1312:19-1313:22).

Dr. Flexner also clarified that the iPrEx study showed only a 44% efficacy rate at preventing HIV infection. (Tr. 1314:24-1315:14). Contrary to Dr. Grant's claim of "an abundance of skepticism" about PrEP (Tr. 1230:2-1231:13), Dr. Flexner testified that skepticism in the field was not about efficacy, but about whether people would take it properly or would engage in more risky behavior (Tr. 1315:15-22, 1319:8-1320:2, 990:14-991:8; *see also* Tr. 768:1-769:4 & 475:8-25 (testimony from Mr. Alton and Dr. Birnkrant discussing Gilead's concerns that Truvada® for PrEP would encourage disinhibition or improper use)). In addition, doctors, including Dr. Grant, published articles in 2005 encouraging the use of PrEP, providing evidence that it worked as expected. (*See, e.g.*, Tr. 1315:23-1319:7; DTX-246 (article by Dr. Grant and 17 others); DTX-247 (article by Dr. Coates)).

Similarly, the jury could have attributed the commercial success of Truvada® and Descovy® for PrEP to factors described by Dr. Flexner, such as the products' excellent safety, efficacy, and tolerability, or advertising (Tr. 1321:14-1322:20) and rejected Dr. Grant's assertion that Gilead's profits show the invention's novelty (Tr. 1232:11-24). Likewise, the jury could have credited Dr. Flexner's testimony that any alleged copying was of "ideas that were already out there before the government even initiated its experiments with monkeys." (Tr. 1320:17-1321:3). The jury was free to conclude that the monkey study built on information known in publications like Tsai 1995, the 2004 Truvada® Label, and CA PEP, among others. Finally, the jury could have found that any long-felt need for prevention was not met by the claimed invention, but by others, including Dr. Grant, who proposed studying Truvada® for PrEP in 2004, and Dr. Conant, who

was already prescribing it to his patients. (Tr. 991:9-19). As Dr. Flexner recounted, the contemporaneous invention of the use of Truvada® for PrEP by Dr. Grant, Dr. Conant, and Dr. Kaldor confirms the claims' obviousness. (Tr. 991:20-992:9); *see Regents of the Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1295 (Fed. Cir. 2018) ("Simultaneous invention may serve as evidence of obviousness when considered in light of all of the circumstances."). For these reasons, the jury's obviousness verdict is amply supported and reflects factual determinations within the province of the jury.

c. Enablement

The jury found that claim 18 of the '423 Patent was not enabled. A patent is enabled when its specification describes the claimed invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to make and use the invention." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 612 (2023) (quoting 35 U.S.C. § 112(a)). To satisfy section 112 of the Patent Act, the specification must enable a person of ordinary skill in the art to make and use the claimed invention. 35 U.S.C. § 112(a); *Union Pac. Res. Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 690 (Fed. Cir. 2001). A patent need not "describe with particularity how to make and use every single embodiment within a claimed class." *Amgen*, 598 U.S. at 610–11. Rather, "a specification may call for a reasonable amount of experimentation to make and use a patented invention." *Id.* at 612. To establish a lack of enablement, "a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without 'undue experimentation.'" *Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014) (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

Plaintiff argues that claim 18 of the '423 Patent is enabled and that the jury's finding otherwise is unreasonable. In support, it characterizes Dr. Flexner's testimony on enablement as

"conclusory" and lacking in evidentiary support. (D.I. 487 at 28-29). To the contrary, Dr. Flexner testified that the specification did not enable a skilled artisan to carry out the claimed PrEP method using all "tenofovir prodrugs" because that term applies to a "family of chemicals," which would include "thousands or tens of thousands of possible prodrug candidates." (Tr. 994:19-995:3). In addition, he addressed the eight *Wands* factors and discussed why each factor supports a finding that claim 18 is not enabled. (Tr. 995:4-998:5; *see also* DDX-3.33 (Dr. Flexner's demonstrative slides)); *In re Wands*, 858 F.2d at 736-37. He described the claim's scope as "incredibly broad" due to its recitation of "tenofovir prodrugs," and that "an enormous amount of experimentation" would be required to determine which tenofovir prodrugs would work in the claimed method. (Tr. 995:15-24, 997:19-22). He also testified that the '423 Patent provides "essentially no guidance or direction" on how to make that determination, and only one working example. (Tr. 995:25-996:15). As to the nature of the invention, Dr. Flexner noted that the claim involved a "process for inhibiting a life-threatening infection." (Tr. 996:16-20). He also testified that the state of the prior art, the relative skill in the art, and the predictability of the art supported finding non-enablement. (Tr. 996:21-997:18). Notably, the Government did not cross-examine Dr. Flexner about enablement at all.

In addition, the Government's expert, Dr. Darren Thakker, acknowledged that different tenofovir prodrugs have different biological properties and toxicity, and that a skilled artisan would need to do experiments to test whether a compound would work as a tenofovir prodrug. (Tr. 1183:12-22). Dr. Thakker also admitted that he had not calculated how many compounds might work as tenofovir prodrugs (Tr. 1184:16-1185:22 ("It could be 10, 20, or it could be more.")). He agreed that the '423 Patent provides only a single working example of a tenofovir prodrug (TDF), and that the patent fails to discuss which categories of tenofovir prodrugs might

be effective for the claimed method or why. (Tr. 1185:23-1186:8). Dr. Thakker also conceded that when he formed his enablement opinions, he was unaware that the CDC scientists performed more experiments in 2016 to determine whether TAF (a tenofovir prodrug) and FTC would work for PrEP – the combination in Descovy® that the Government now asserts claim 18 covers. (Tr. 1190:2-1195:13); *cf. Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1375 (Fed. Cir. 2017) (finding that post-priority-date evidence of potentially undue experimentation was relevant to determining enablement).

To the extent Dr. Thakker's opinions on enablement conflicted with Dr. Flexner's, the jury was entitled to credit Dr. Flexner. *See, e.g.*, *Smith v. Garlock Equip. Co.*, 658 F. App'x 1017, 1027 (Fed. Cir. 2016) (explaining that a "battle of the experts" requires "the fact finder [to] weigh the merits of competing expert testimony"). Thus, the Government has not shown entitlement to JMOL on the issue of enablement of claim 18 of the '423 Patent.

B. Plaintiff's Request in the Alternative for a New Trial

Plaintiff requests a new trial based on this Court's rulings on certain evidence, specifically relating to the exclusion of *Inter Partes Review* (IPR) petitions and the limited admission of the parties' Material Transfer Agreements (MTAs).[5] The parties briefed these issues in their motions *in limine* and argued them at the pretrial conference. (*See* D.I. 434, Exs. 9P.1 & 9D.1; D.I. 447 at 52:5-58:6 & 64:18-65:15). The Court excluded the IPR non-institution proceedings, finding that the minimal relevance of that evidence would be far outweighed by the risk of confusing and prejudicing the jury. (D.I. 447 at 65:11-15). Regarding the MTAs, the Court found that they were relevant to Gilead's noninfringement defenses, specifically whether they had knowledge of

[5] The Court's ruling limited the evidence Defendants could introduce regarding the MTAs to the extent that it related to their argument that they did not have knowledge of infringement. The Court also permitted Plaintiff to raise objections at trial.

infringement, and permitted their admission for that limited purpose. (*Id.* at 57:20-58:6; *see also* D.I. 450 at 3 n.5). Plaintiff argues that the Court erred in both rulings. The Court addresses these arguments below.

1. Exclusion of IPR Petitions

Before trial, Defendants moved to exclude evidence of related agency invalidity proceedings, including the PTAB's IPR non-institution decisions for the asserted patents and the EPO's opposition to a foreign counterpart of the asserted patents. (D.I. 434, Ex. 9D.1 at 1). Defendants argued that admitting such evidence would confuse the jury, have minimal probative value, result in trial delay, and overall, be unfairly prejudicial. (*Id.* at 1-3). The Court granted Defendants' motion, finding that "the minimal relevance of the evidence . . . is far outweighed by the risk of confusing and prejudicing the jury."[6] (D.I. 447 at 65:12-15). Plaintiff now contends that the jury verdict goes against the weight of the evidence and in addition, that Gilead "repeatedly made misleading and confusing statements that left the jury with the incorrect impression that the use of Truvada for PEP, and PEP guidelines, specifically, were never considered by the Patent Office in evaluating the nonobviousness of the asserted claims."[7] (D.I. 487 at 25).

In support of its contention that the jury verdict is against the weight of the evidence, in addition to arguing that the prior art does not render obvious the "thereby" step, Plaintiff argues

[6] IPR institution is a specialized agency determination that does not provide "the benefit of a full adversarial proceeding," because it is based "on a record that [is] less than complete." *ART+COM Innovationpool GmbH v. Google Inc.*, C.A. No. 14-217-TBD, 2016 WL 11531119, at *2 (D. Del. May 16, 2016). Thus, Rule 403 "strongly favors exclusion" because a non-institution "is not a final decision on validity, is based on different legal standards, and has no estoppel effect." *Andover Healthcare, Inc. v. 3M Co.*, C.A. No. 13-843-LPS, 2016 WL 6404111, at *2 (D. Del. Oct. 27, 2016).

[7] Plaintiff moves in the alternative on this ground, seeking judgment as a matter of law on the jury's obviousness verdict.

that because Gilead itself was not interested in pursuing PrEP during the relevant timeframe, 2004-2006, the jury verdict rests on a contradiction. In other words, because Gilead – "one of the major HIV research companies during the relevant timeframe" – did not pursue Truvada® for PrEP, no person of skill in the art would have pursued Truvada® for PrEP. (*See id.*). The Court does not find this argument compelling. As Gilead points out, it is a company. As such, it has concerns that may be different than those of a person of skill in the art, and not confined to skepticism that Truvada® for PrEP would work. Those concerns included that people would not take the drug as instructed (*e.g.*, skip doses) or that it would encourage disinhibition. (*See* Tr. 747:8-748:14 (Mr. Alton discussing Gilead's concern that Truvada® for PrEP would encourage disinhibition), Tr. 768:1-769:4 (Mr. Alton discussing Gilead's concern that patients would take the drugs "episodically"), Tr. 475:8-25 (Dr. Birnkrant admitting that Gilead did not pursue indication in part because it was concerned about encouraging disinhibition), Tr. 1319:8-1320:2 (Dr. Flexner explaining that Gilead's hesitation to pursue a PrEP indication was unrelated to efficacy)).

Plaintiff also argues that Gilead misled the jury to believe that PEP guidelines were never considered by the Patent Office in evaluating the nonobviousness of the Asserted Claims. (D.I. 487 at 25). Plaintiff further complains that due to the Court's pretrial ruling, it was unable to cross-examine Dr. Flexner on the guidelines presented before the PTO and those relied on by Gilead at trial, which the Government contends are materially similar. (*Id.* at 26).

Gilead emphasizes that its statements and those of its witnesses concerned the patent examiner not the Office. Thus, Gilead argues that it did not improperly open the door to the IPR proceedings and further that the Government forfeited its argument by failing to seek reconsideration of the *in limine* ruling at trial. (D.I. 489 at 27-28). In reply, Plaintiff argues that it was not required to reraise its objection at trial because the Court granted Defendants' motion *in*

limine. (D.I. 490 at 15 (citing *Walden v. Georgia-Pacific Corp.*, 126 F.3d 506, 519 (3rd Cir. 1997))). The Court agrees to the extent that the Government's objection would be the same as it was prior to trial. To the extent that the objection is based on a change of circumstance, such as in response to evidence or testimony elicited by Defendants during trial, the Government should have sought reconsideration of the Court's *in limine* ruling.[8] Ultimately, because the Court does not find that Gilead mislead or confused the jury to such an extent as to justify a new trial, that the Government never reraised its objection is of little matter.

2. Admission of MTAs

Ahead of trial, Plaintiff moved *in limine* to exclude evidence, testimony, and argument regarding the MTAs, as well as other agreements.[9] Plaintiff argued that allowing such evidence would be highly prejudicial and had no probative value. (D.I. 434, Ex. 9P.1 at 1-3). The Court denied Plaintiff's motion in part, finding that such evidence was relevant to "questions with respect to inducement," D.I. 447 at 57, which includes both knowledge of infringement and intent to induce. Now, Plaintiff reiterates its earlier argument. Although Plaintiff construes it broadly, stating that "the Court denied the Government's motion to preclude Gilead from offering arguments and testimony about breach of contract issues," the brunt of its argument is that

[8] *See, e.g.*, 2 Michael H. Graham, Handbook of Federal Evidence § 103:8 (9th ed. 2022) ("If the relevant facts and circumstances change materially after the advance ruling has been made, those facts and circumstances cannot be relied upon on appeal unless they have been brought to the attention of the trial court by way of a renewed, and timely, objection, offer of proof, or motion to strike.").

[9] By way of background, between 2004 and 2008, Gilead and the CDC executed several MTAs, pursuant to which Gilead provided the CDC with FTC, tenofovir, and tenofovir disoproxil fumarate (TDF), a tenofovir prodrug. Under the terms of the MTAs, CDC was to "promptly disclose to [Gilead] all results, data, and other information or materials derived from" any materials and confidential information provided by Gilead, as well as to "promptly notify [Gilead] of any Inventions." (D.I. 1 ¶¶ 122–23).

discussion of the notice provision in the MTAs confused the jury, specifically regarding the issue of whether Defendants had actual knowledge of the patents. Plaintiff further contends that by allowing Gilead to argue that the United States failed to promptly notify Gilead, per the MTAs, the Court in effect permitted Gilead to indicate that Plaintiff had behaved unethically and unfairly, which accordingly, was highly prejudicial. (D.I. 487 at 30). In response, Gilead argues that the Court's pretrial ruling was correct and that its introduction of evidence of and testimony about the MTAs and related argument was proper. (D.I. 480 at 29).

Gilead also points out that Plaintiff failed to raise any objections to the admission of the now-complained-of evidence, testimony, or argument at trial. Plaintiff argues in reply that it did not need to reraise its objections because the Court limited the issues to be revisited in its Order After Pretrial Conference, D.I. 450. In that Order, the Court clarified that "Defendants may introduce evidence related to the material transfer agreements at trial to the extent that it relates to their argument that they did not have knowledge of infringement," but "may not introduce the evidence to argue their unenforceability defenses before the jury." (D.I. 450 at 3 n.5). Prior to the issuance of this order, during the pretrial conference, the Court told Plaintiff that it could raise objections related to the MTAs during the trial. (D.I. 447 at 58 ("[I]f there is an objection that [the Court] need[s] to deal with in a particular context in realtime, you can raise that at the trial."); *see also id.* at 57-58 ("[W]hen we're in the middle of trial . . . if you have an objection [to the MTAs], you can make the objection.")). The government forfeited any argument that Gilead strayed beyond the permissible use of the MTAs by failing to object at trial.

Plaintiff references a discussion the Court had with the parties outside the presence of the jury as indicative of the Court's "concern for juror confusion based on Gilead's presentation of MTA issues." (D.I. 487 at 30 (citing Tr. 536:25–544:23)). That much is true – the Court did press

the parties, particularly Gilead, on the relevance of the notice provision of the MTAs. In fact, at that time, Plaintiff objected to an exhibit proffered by Gilead, which resulted in a discussion of how the issue of notice was being presented to the jury and the related risk of confusing the jury, and the Court sustained the objection. (Tr. 534:18-541:18).

Plaintiff also argues that Gilead elicited the MTA evidence and testimony improperly, "permeat[ing] the record with irrelevant, misleading, and confusing allegations about breach of contract". (D.I. 487 at 30 (citing examples without explanation, none of which it raised in its motion *in limine* nor objected to at trial)). Gilead maintains that it introduced the MTAs at trial for the purposes of providing direct evidence of its intent to protect itself from infringement liability and of its justified, good-faith belief that selling its products in fact did not infringe any government patents.[10] (*See, e.g.*, Tr. 849:7-12 (Dr. Rooney testifying that Gilead believed its actions did not induce infringement because it "trusted" that "the CDC would adhere to its obligations to promptly notify Gilead of any inventions" relating to the MTAs)). In addition, Gilead argues that the MTAs were relevant to other issues, including why Dr. Conant did not have specific patient records that would further corroborate his testimony, the credibility of government witnesses like Dr. Heneine, and damages (*i.e.*, to show how Gilead's situation was unique from other licensees). (Tr. 289:25-290:14, 674:2-681:15, 697:7-699:19, 792:8-793:5). Plaintiff does not contest the propriety of these other uses. In fact, following cross-examination, the United States questioned one of its witnesses, Dr. Heneine, regarding notice, specifically whether he felt like he had given notice to Gilead through the competing interest section of an article he co-authored. (Tr. 349:12-350:2; 379:6-13). Plaintiff was able to address issues of notice with their

[10] *See Roche Diags. Corp. v. Meso Scale Diags.*, 30 F.4th 1109, 1118-19 (Fed. Cir. 2022). (holding a good-faith belief in freedom to operate defeats inducement liability, even where that belief is based on erroneous interpretation of an agreement).

witnesses and was not unfairly prejudiced. And the Court does not find that the admission of evidence and testimony and related argument regarding the MTAs justifies a new trial.

The Court has already found that substantial evidence supports the jury's verdict on invalidity. For the same reasons, the Court concludes that the jury's verdict was not against the weight of the evidence, even without viewing the evidence most favorably to Defendants. That is, Plaintiff has failed to show that "a miscarriage of justice would result if the verdict were to stand," that the verdict "cries out to be overturned" or that the verdict "shocks [the] conscience." *Williamson*, 926 F.2d at 1352-53.

3. Conditional Ruling on a New Trial Under Rule 50(c)(1)

Rule 50(c)(1) provides that, "[i]f the court grants a renewed motion for judgment as a matter of law, it must also conditionally rule on any motion for a new trial by determining whether a new trial should be granted if the judgment is later vacated or reversed." Fed. R. Civ. P. 50(c)(1). Should the Federal Circuit later reverse or vacate the grant of judgment as a matter of law on direct infringement, there would be no need for a new trial as the Federal Circuit would, in essence, be upholding a finding of no infringement. Similarly, if the Federal Circuit should later reverse as to all grounds of invalidity but not this Court's grant of judgment as a matter of law on direct infringement, this Court believes that a new trial on the issue of induced infringement is warranted.

III. CONCLUSION

For the foregoing reasons, Defendants' renewed motion for judgment as a matter of law or, in the alternative, a new trial (D.I. 487) is GRANTED-IN-PART and DENIED-IN-PART. An appropriate Order will follow.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA,	)	
	)	
Plaintiff/Counterclaim Defendant,	)	
	)	
v.	)	
	)	
GILEAD SCIENCES, INC.,	)	C.A. No. 19-2103 (MN)
	)	
Defendant/Counterclaim Plaintiff,	)	
	)	
and GILEAD SCIENCES IRELAND UC,	)	
	)	
Defendant.	)	

ORDER

At Wilmington this 22nd day of March 2024:

For the reasons set forth in the Memorandum Opinion issued this date, IT IS HEREBY ORDERED that:

1. Plaintiff's renewed motion (D.I. 487) for judgment as a matter of law or, in the alternative, for a new trial is GRANTED-IN-PART and DENIED-IN-PART; and

2. The judgment on the jury verdict (D.I. 471) is PARTIALLY VACATED as to Defendants' liability for direct infringement and judgment as a matter of law will be entered in Plaintiff's favor on this theory of liability.

Maryellen Noreika

The Honorable Maryellen Noreika
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA,	)	
	)	
Plaintiff/Counterclaim Defendant,	)	
	)	
v.	)	
	)	
GILEAD SCIENCES, INC.,	)	C.A. No. 19-2103 (MN)
	)	
Defendant/Counterclaim Plaintiff,	)	
	)	
and GILEAD SCIENCES IRELAND UC,	)	
	)	
Defendant.	)	

FINAL JUDGMENT

This 22nd day of March 2024, the Court having held a jury trial and the jury having rendered a unanimous verdict on May 9, 2023 (*see* D.I. 468, 469), pursuant to Rule 58(b) of the Federal Rules of Civil Procedure, IT IS HEREBY ORDERED that:

1. Judgment is entered in favor of Plaintiff and against Defendants as to direct infringement of the asserted claims[1] for both Truvada® for PrEP and Descovy® for PrEP.

2. Judgment is entered in favor of Defendants and against Plaintiff that all of the asserted claims are invalid on the bases of anticipation and obviousness and that claim 18 of the '423 Patent is also invalid for lack of enablement.

IT IS FURTHER ORDERED that the deadline for any party to move for costs and attorneys' fees (including under 35 U.S.C. § 285) is extended to the later of thirty (30) days after

[1] The asserted claims are claim 13 of U.S. Patent No, 9,579,333, claim 18 of U.S. Patent No. 9,937,191, and claim 18 of U.S. Patent No. 10,335,423 ("the '423 Patent").

the time for appeal has expired or thirty (30) days after issuance of the mandate from the appellate court, and no party shall file any such motion before that time.

Maryellen Noreika

The Honorable Maryellen Noreika
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA,	)	
	)	
Plaintiff/Counterclaim Defendant,	)	
	)	
v.	)	
	)	
GILEAD SCIENCES, INC.,	)	C.A. No. 19-2103 (MN)
	)	
Defendant/Counterclaim Plaintiff,	)	
	)	
and GILEAD SCIENCES IRELAND UC,	)	
	)	
Defendant.	)	

ORDER

At Wilmington this 9th day of May 2024:

IT IS HEREBY ORDERED that:

1. Defendants' Motion to Amend Judgment Pursuant to Fed. R. Civ. P. 59(e) (D.I. 500) is DENIED. Defendants have not satisfied the standard for granting a Rule 59(e) motion. *See Lazaridis v. Wehmer*, 591 F.3d 666, 669 (3d Cir. 2010).

2. Pursuant to Rule 60(a), a court may *sua sponte* correct an oversight or omission in a judgment. To the extent that the Final Judgment (D.I. 498) omits context and suggests it is inconsistent with this Court's Memorandum Opinion (D.I. 496), the Court will clarify its judgment as to direct infringement. This correction does not affect the substantive rights of the parties and required no "cerebration or research into the law or planetary excursions into facts[.]" *See Pfizer Inc. v. Uprichard*, 422 F.3d 124, 130 (3d Cir. 2005).

An Amended Final Judgment will follow.

Maryellen Noreika

The Honorable Maryellen Noreika
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE UNITED STATES OF AMERICA,	)	
	)	
Plaintiff/Counterclaim Defendant,	)	
	)	
v.	)	
	)	
GILEAD SCIENCES, INC.,	)	C.A. No. 19-2103 (MN)
	)	
Defendant/Counterclaim Plaintiff,	)	
	)	
and GILEAD SCIENCES IRELAND UC,	)	
	)	
Defendant.	)	

AMENDED FINAL JUDGMENT

This 9th day of May 2024, the Court having corrected an oversight in the March 22, 2024 Final Judgment (D.I. 498) pursuant to Rule 60(a) of the Federal Rules of Civil Procedure, IT IS HEREBY ORDERED that:

1. Judgment is entered in favor of Plaintiff and against Defendants that one or more patients or physicians (either separately or jointly) directly infringed the asserted claims[1] for Truvada® for PrEP and for Descovy® for PrEP.

2. Judgment is entered in favor of Defendants and against Plaintiff that all of the asserted claims are invalid on the bases of anticipation and obviousness and that claim 18 of the '423 Patent is also invalid for lack of enablement.

IT IS FURTHER ORDERED that the deadline for any party to move for costs and attorneys' fees (including under 35 U.S.C. § 285) is extended to the later of thirty (30) days after

[1] The asserted claims for Truvada® are claim 13 of U.S. Patent No, 9,579,333, claim 18 of U.S. Patent No. 9,937,191, and claim 18 of U.S. Patent No. 10,335,423 ("the '423 Patent") The asserted claim for Descovy® is claim 18 of the '423 Patent.

the time for appeal has expired or thirty (30) days after issuance of the mandate from the appellate court, and no party shall file any such motion before that time.

The Honorable Maryellen Noreika
United States District Judge

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District of Delaware

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US009044509B2

(12) **United States Patent**
Heneine et al.

(10) **Patent No.: US 9,044,509 B2**
(45) **Date of Patent: Jun. 2, 2015**

(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS**

(75) Inventors: **Walid M. Heneine**, Atlanta, GA (US); **Thomas M. Folks**, Helotes, TX (US); **Robert Janssen**, Atlanta, GA (US); **Ronald Otten**, Villa Rica, GA (US); **Jose Gerardo Garcia Lerma**, Villa Rica, GA (US)

(73) Assignee: **The United States of America, as represented by the Secretary, Department of Health and Human Services**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1309 days.

(21) Appl. No.: **11/669,547**

(22) Filed: **Jan. 31, 2007**

(65) **Prior Publication Data**

US 2007/0265227 A1 Nov. 15, 2007

Related U.S. Application Data

(60) Provisional application No. 60/764,811, filed on Feb. 3, 2006.

(51) **Int. Cl.**
A61K 31/675 (2006.01)
A61K 31/505 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61K 45/06*** (2013.01); *A61K 31/675* (2013.01); *A61K 31/513* (2013.01); ***A61K 31/7072*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/675; A61K 31/513; A61K 2300/00
USPC 514/274, 86
See application file for complete search history.

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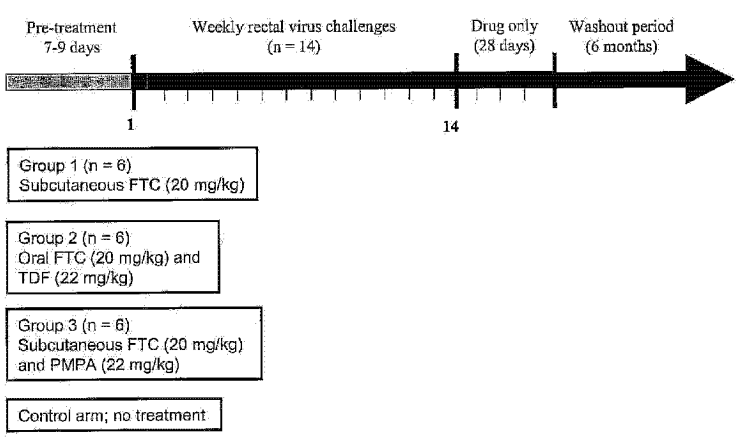
Primary Examiner — Shengjun Wang
(74) *Attorney, Agent, or Firm* — Klarquist Sparkman, LLP

(57) **ABSTRACT**

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose within 24 hours of the exposure. A regime of regular daily doses is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection the detailed combination prior to sexual exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

18 Claims, 4 Drawing Sheets



(51) **Int. Cl.**

A61K 45/06	(2006.01)
A61K 31/7072	(2006.01)
A61K 31/513	(2006.01)

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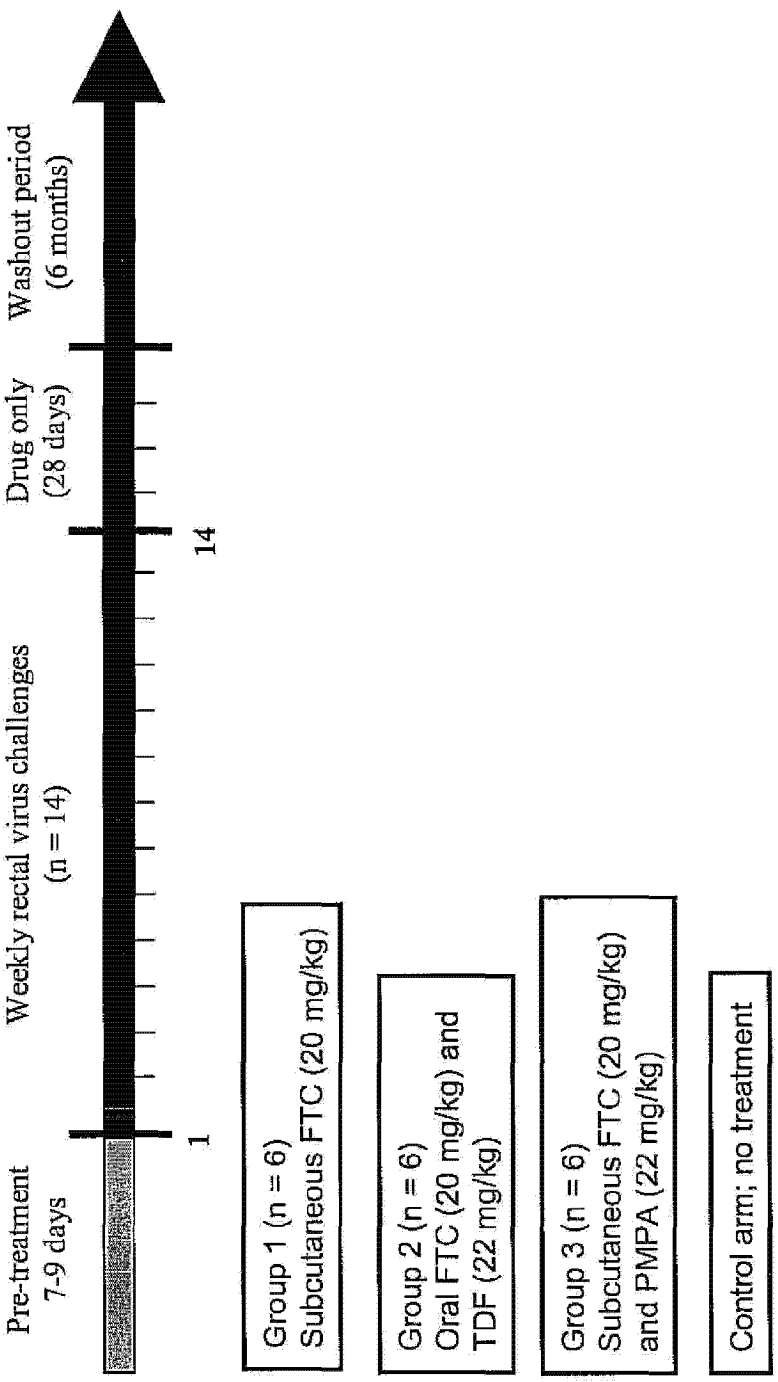
Pre-treatment
7-9 days
Weekly rectal virus challenges
(n = 14)
Drug only
(28 days)
Washout period
(6 months)
1
14
Group 1 (n = 6)
Subcutaneous FTC (20 mg/kg)
Group 2 (n = 6)
Oral FTC (20 mg/kg) and
TDF (22 mg/kg)
Group 3 (n = 6)
Subcutaneous FTC (20 mg/kg)
and PMPA (22 mg/kg)
Control arm; no treatment

Fig 1.

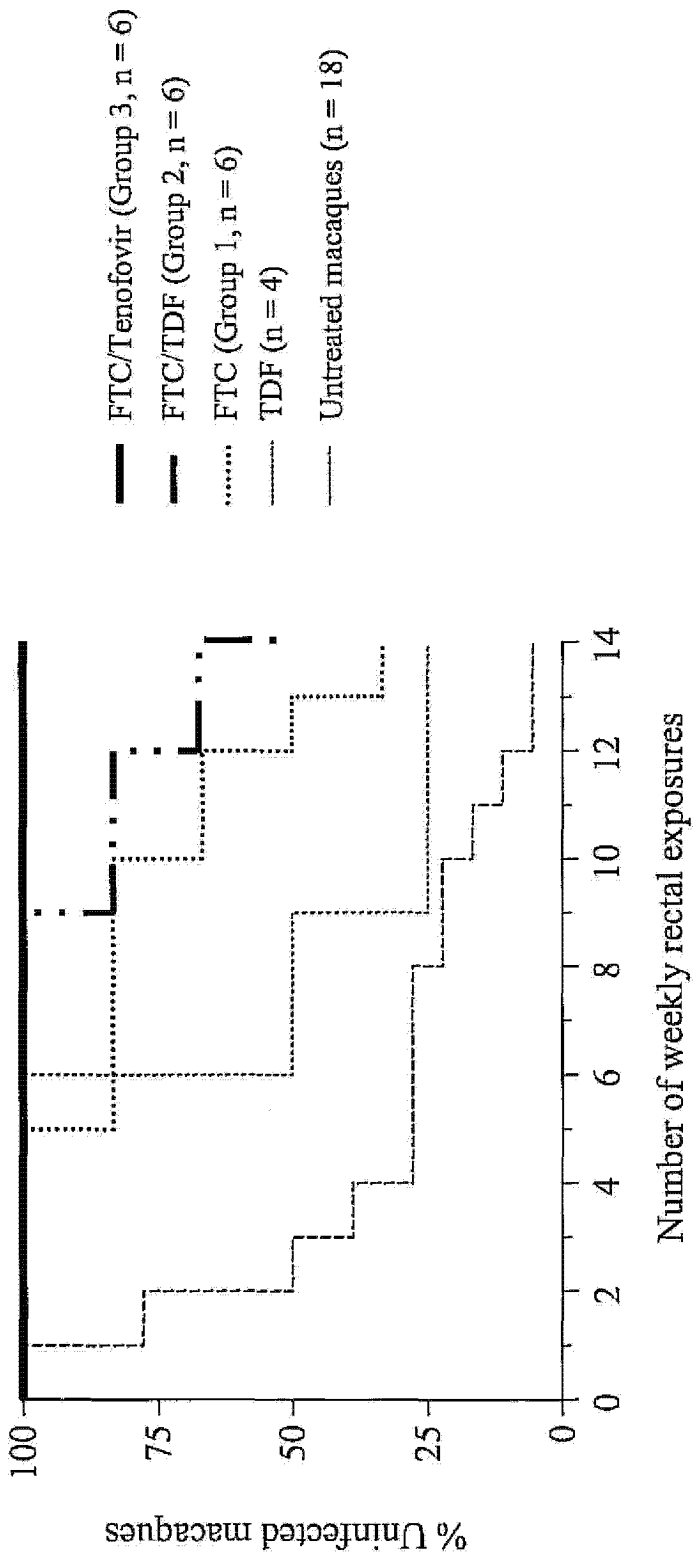

Fig 2.

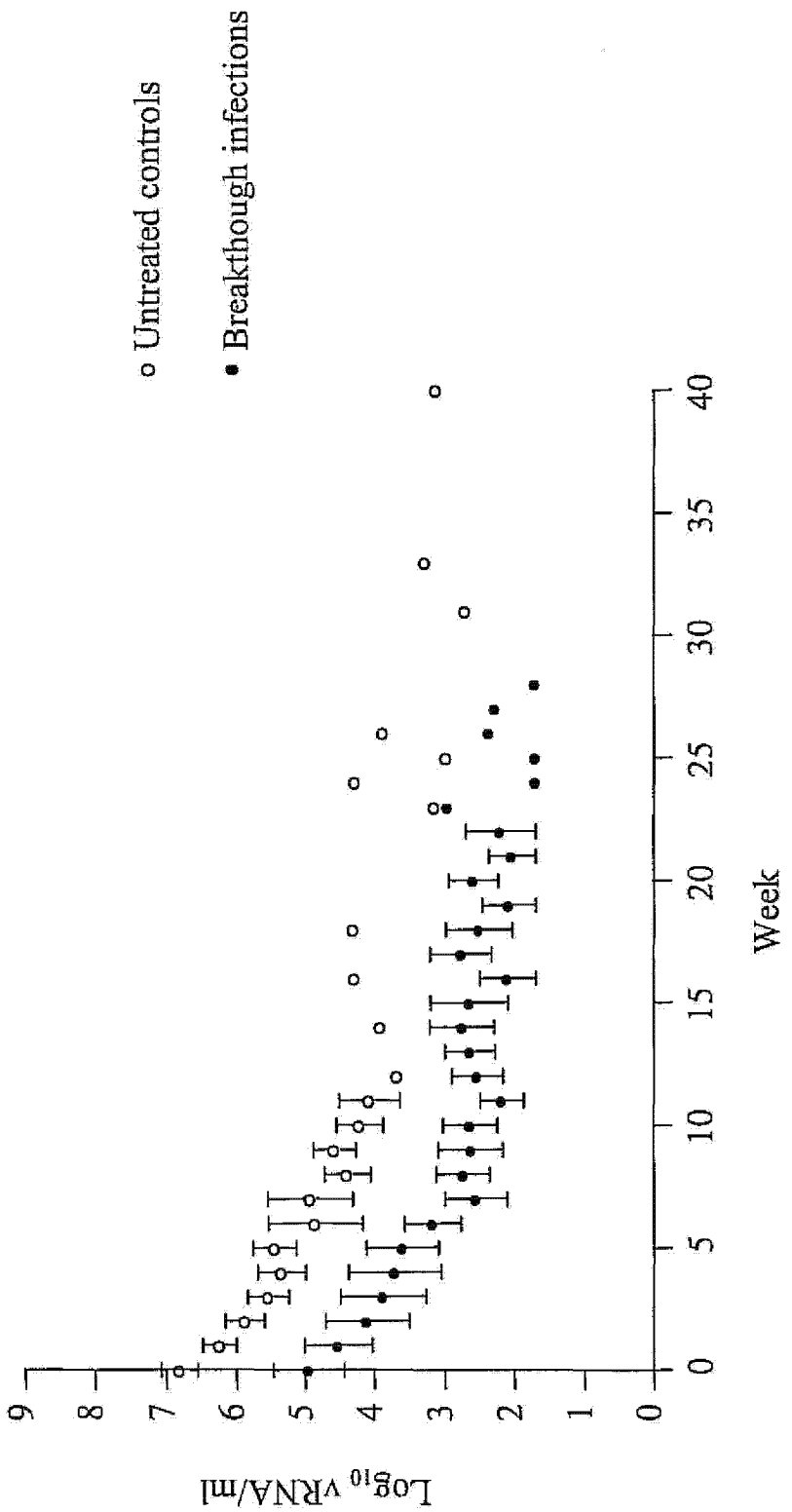
o Untreated controls
• Breakthough infections
Log10 vRNA/ml
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30
35
40
Week

Fig. 3.

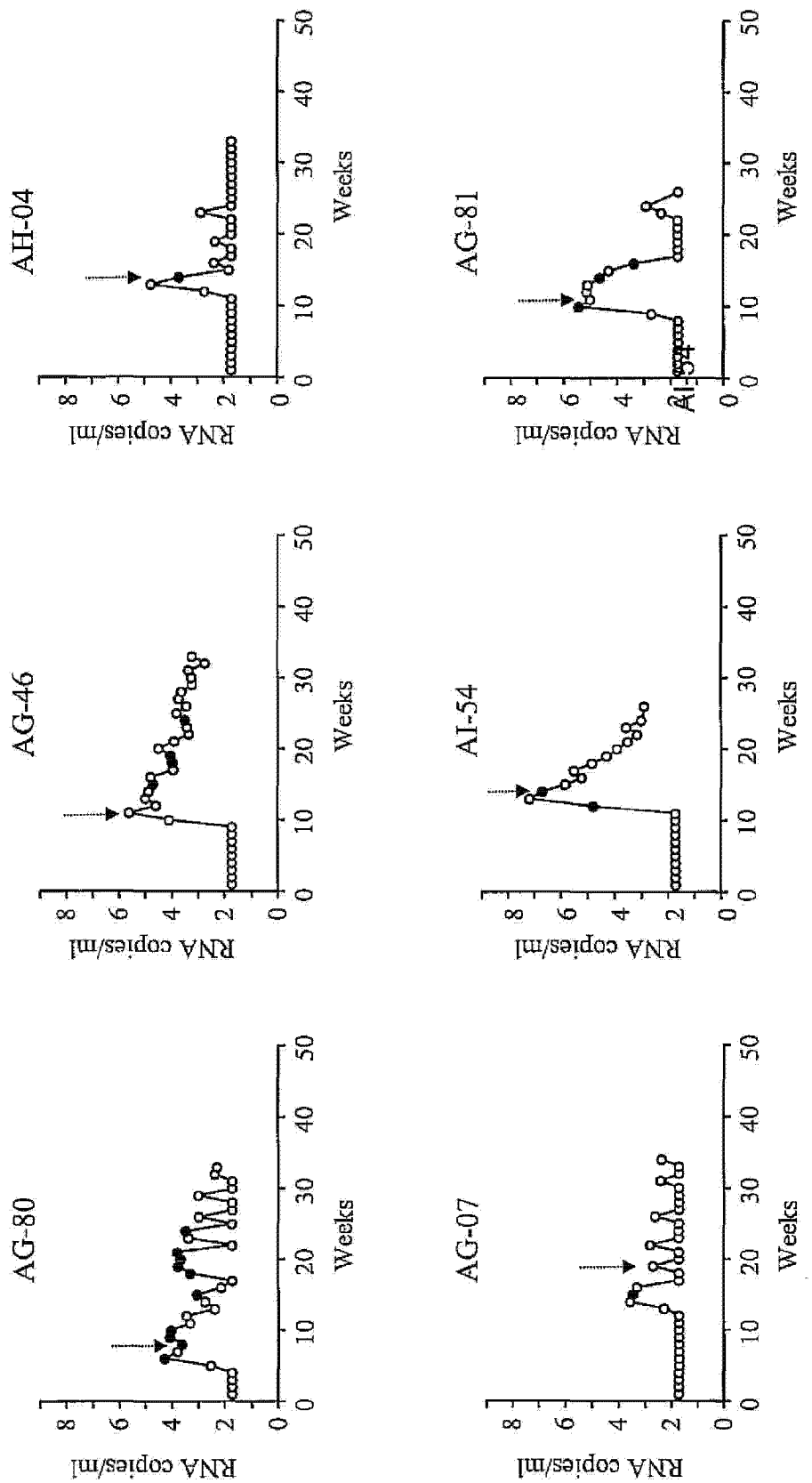
AH-04
AG-81
AG-46
AI-54
AG-80
AG-07
RNA copies/ml
Weeks
0
2
4
6
8
0
10
20
30
40
50

Fig. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority of U.S. Provisional Patent Application Ser. No. 60/764,811 filed Feb. 2, 2006, which is incorporated herein by reference.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

The present invention in general relates to a process for inhibiting initial infection by a retrovirus such as human immunodeficiency virus (HIV) and in particular to a combination of a nucleoside reverse transcriptase inhibitor (NRTI) and a nucleotide reverse transcriptase inhibitor (NtRTI) capable of preventing self-replicating retroviral infection, even in response to multiple viral challenges.

BACKGROUND OF THE INVENTION

Despite the fact that significant progress has been made slowing the advancement of the symptoms of AIDS associated with HIV infection, in the absence of an effective vaccine, HIV continues to spread globally. The spread of HIV persists in part because an infected individual remains a potential source of injection. It is clear that current treatment of monitoring viral titer and in response to a titer exceeding a preselected threshold commencing treatment with highly active antiretroviral therapy (HAART) has not prevented new infections.

An attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment. As HIV and, in particular HIV-1, often begins with a comparatively small population of retroviral particles being transmitted to a new host and within a few days self-replicating into a retroviral titer detectable in host blood serum. 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.

Previous attempts at pre-exposure prophylaxis have met with limited success. Prophylactic activity has been demonstrated with the NtRTI, tenofovir in monkey models challenged with simian immunodeficiency virus (SIV).[1-3] Unfortunately, oral daily dosing and pre-exposure prophylaxis with tenofovir at a dose equivalent to that used in humans proved to only be partially protective against rectal SHIV transmission.[4]

HAART therapy involves the administration of a combination including at least three active compounds classified by the mode of operation as an NRTI, an NtRTIs, a non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitor, and an entry inhibitor. While HAART is effective in lowering retroviral titer in a host, concerns remain as to the long term toxicity and the retained potential to infect others. It is also unknown if initiating HAART therapy in a pre-exposure prophylactic regimen would be efficacious. As a result, society remains devoid of a pre-exposure prophylactic regimen to prevent an individual from developing self-propagating retrovirus infection subsequent to initial exposure.

Thus, there exists a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population. There also exists a need for a chemoprophylactic composition formulated with a vehicle amenable to user compliance.

SUMMARY OF THE INVENTION

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose prior to the exposure. A regime of multiple temporally spaced doses prior to retroviral exposure is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection a combination of a pharmaceutically effective nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

A kit is also provided that includes at least one combination dose of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor sufficient to protect a primate host from developing a self-replicating retroviral infection along with instructions for the administration of the at least one dose one prior to and optionally one additional dose subsequent to a potential exposure to an immunodeficiency retrovirus along with dosing modifications associated with subject characteristics and behaviors to further reduce the risk of contracting a self-replicating immunodeficiency retrovirus infection.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic depicting one study of the present invention for 4 groups of macaques in which all treated macaques received known antiretroviral medications 7 to 9 days prior to the first virus inoculation and continuing throughout the study with treated animals that remained uninfected throughout the 14 viral challenges receiving 28 additional days of post-exposure prophylactics.

FIG. **2** is a survival curve graph for macaque Groups 1-4 per FIG. **1**, as well as for animals receiving only tenofovir disoproxil fumarate (TDF).

FIG. **3** is a graph depicting a plot of viremia as a function of time for untreated controls (○) and breakthrough infections (●) where each point represents a mean viremia observed, 0 time indicates peak plasma virus load observed in a given animal where the arrow bars denote standard error of the mean (SEM).

FIG. **4** depicts plots of infection dynamics as a function of time during the study per FIG. **1** with plots for animals coded as AG-80, AG-46, AH-04 and AG-07 corresponding to emtricitabine (FTC) treatment alone, or FTC plus TDF treatment (AI-54 and AG-81). The arrow indicates the first detectable antibody response. Grey circles indicate detectable

M184V/I mutation; wild type sequences are shown in as black full circles. Open circles indicate the time points where no genotype was undertaken.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention has utility in protecting a primate host from self-propagating immunodeficiency virus infection. The use of a combination of antiretroviral agents as a prophylactic dosing regime is also provided for the manufacture of a medicament is provided for protection against a human immunodeficiency virus infection developing to a level of self-replicating infection. Retroviral transmission through most routes entails a new primate host receiving a small number of viral particles. Common routes of retrovirus transmission illustratively include sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, blood transfusions, birth canal exposure, breastfeeding, and transplacental contact between individuals. Through the administration of at least one nucleoside reverse transcriptase inhibitor (NRTI) and at least one nucleotide reverse transcriptase inhibitor (NtRTI) prior to a retrovirus exposure protection is provided against development of a self-replicating retroviral infection. As the aforementioned exposure routes are characterized by a small number of retrovirus particles being transferred to the new primate host, this initial phase of infection represents a window of opportunity to protect a host from infection. The inventive chemoprophylactic treatment is provided through a dosing regimen. A dosing regimen according to the present invention that provides retroviral protection to a host primate includes at least one single dose administered prior to initial retroviral exposure. An inventive dosing regimen also includes a course of multiple doses administered in advance of exposure to maintain a therapeutic level of NRTI and NtRTI agents in the primate host. The timing of the at least one does prior to retroviral exposure is dictated by the pharmacokinetics of the NRTI and NtRTI components to assure the presence of a therapeutically effective amount of inventive composition for at least 20 hours subsequent to the exposure to the communicated small retroviral particle population. Multiple doses are administered according to the present invention at regular time intervals and amounts such as for example like formulated daily doses for a period of several days, weeks, or months; or are administered in advance of a likely exposure as a cluster of doses, with the amount of NRTI and NtRTI components in each dose being independent of the of amount of NRTI and NtRTI in other doses within the cluster. While most oral, topical, and parenteral existing versions of NRTIs and NtRTIs are fully absorbed and therapeutically active within 1 to 8 hours, it is appreciated that subcutaneous implants and long acting timed release formulations allow for a single dose to sustain therapeutically effective amounts of an inventive prophylactic composition for several days, weeks, or even months. Representative of sustained release compositions and implants are provided in the U.S. Pat. Nos. 4,122,129; 4,927,687; 4,996,047; 5,169,642; and 5,656,296.

The combination of NRTI and NtRTI compounds administered prophylactically according to the present invention are shown to provide a dose-dependent inhibition of HIV self-replicating infection and a therapeutically effective dosing primate host protection against self-replicating HIV infection is provided, even in response to multiple viral challenges. While the present invention is largely detailed with respect to HIV-1 as a prototypical infectious and pathogenic retrovirus, it is appreciated that other retroviruses owing to reliance on reverse transcription for replication are also protected against in a primate host according to the present invention.

As used herein, "protection" as used in the context of a host primate response to an immunodeficiency virus challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.

As used herein, the term "retrovirus" is inclusive of any virus that utilizes reverse transcriptase in the viral replication cycle and therefore is susceptible to the antiviral activity of nucleoside or nucleotide analogs specifically inclusive of HIV (HIV-1 and HIV-2), HTLV-1, HTLV-2, HTLV-3, HTLV-4, and SIV. Also encompassed are viruses such as HBV that although not technically classified as retroviruses nonetheless utilize a reverse transcriptase and are therefore susceptible to the antiviral activity of nucleoside and/or nucleotide analogs.

As used herein a "primate host" is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Nonhuman primates are appreciated to themselves be susceptible to infection by retroviruses and in particular immunodeficiency viruses and represent well-established animal models as to human response with an appreciation that physiological differences often require different doses in milligrams per kilogram for a nonhuman primate animal model relative to a human.

The compositions of the present invention include administration in combination of an NRTI and NtRTI and are readily compounded by pharmaceutical composition with conventional pharmaceutically acceptable carriers or diluents. Additionally, pharmaceutically acceptable derivatives and prodrugs of active NRTIs and NtRTIs operative in the present invention include salts such as alkali metal salts; esters such as acetate, butyrate, octinoate, palmitate, chlorobenzoates, benzoates, C_1-C_6 benzoates, succinates, and mesylate; salts of such esters; and nitrile oxides. It is appreciated that other analogs of pharmaceutically active NRTIs or NtRTIs that provide within a primate host an active antiviral metabolite residue are also suitable as part of an inventive composition. A pharmaceutically acceptable carrier or diluent includes agents that are compatible with other ingredients of a dosage and not injurious to a primate host. The identity and process for compounding a combination of at least one NRTI and at least one NtRTI into a dosage form suitable for delivery by a route with administration by oral, rectal, topical, vaginal or parenteral routes of administration are provided in Remington's Science and Practice of Pharmacology, 20th Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

As used herein the term "prodrug" is defined to include a compound that when administered to a primate host generates an active NRTI or NtRTI as a result of spontaneous reaction under physiological conditions, enzymatic catalysis, metabolic clearance, or combinations thereof. An exemplary NtRTI prodrug currently FDA approved for HAART use is tenofovir disoproxil fumarate (TDF) and is detailed in U.S. Pat. No. 5,935,946.

The present invention provides an alternative to conventional retroviral therapy using HAART, in response to self-propagating HIV infection by protecting a primate host against the establishment of self-replicating retroviral infection that provides an indication for such therapy. Through prophylactic prior dosing with an inventive combination including at least one NRTI and one NtRTI, replication of the comparatively low number of viral particles received by a host primate is prevented.

To achieve protection against a primate host developing a retroviral self-replicating infection, at least one dosage of an NRTI and NtRTI is administered to the primate host prior to exposure to the retrovirus. Preferably, the at least one NRTI and at least one NtRTI are administered concurrently. More preferably, the combination of reverse transcriptase inhibitors is compounded into a single formulation.

The process of the present invention demonstrates protection against retroviral self-replicating infection through administration of even a single dosage administered prior to the retroviral exposure. Owing to the known pK rates of specific NRTIs and NtRTIs, a single dosage is administered to assure a therapeutically effective amount of NRTI and NtRTI persist in the primate host for a time of more than 12 hours after viral challenge. With conventional NRTI and NtRTI formulations, currently approved for HAART, preferably an inventive dose is administered within 12 hours prior to retroviral exposure and still more preferably often within 2 hours prior to retroviral exposure. The practice of the inventive process involving the administration of a single dosage in the hours proceeding a likely retroviral exposure is particularly advantageous in assuring compliant dosing in a human and also avoids side effects associated with a regular dosing regime and is particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure. Preferably, an additional dose or doses of a combination of at least one NRTI and at least one NtRTIs is provided subsequent to the retroviral exposure event to assure adequate antiviral reverse transcriptase inhibitor concentration during and immediately subsequent to retroviral infection of the host founder cell population so as to preclude retroviral self-replication to assure NRTI and NtRTI incorporation into a replicating virus genome. Preferably, a dose of an inventive composition taken after retroviral exposure is administered within 24 hours subsequent to the exposure, and more preferably within 12 hours subsequent to the exposure.

Alternatively, an individual routinely subjected to retroviral exposure can be protected against the development of a self-replicating retroviral infection through administration of regular prophylactic doses of an inventive combination. As a result, an epidemiological advantage exists in controlling the outbreak and spread of a retrovirus within a population is provided through offering routine doses of an inventive composition prophylactically to high-risk persons such as sex workers and a short course prophylactic inventive composition to uninfected sex trade clientele.

It is appreciated that hybrid dosing regimes of an inventive composition are also operative herein and include multiple doses prior to retroviral exposure with multiple doses not being administered for a duration or with sufficient periodicity to arise to the level of a routine prophylactic regime.

The at least one nucleoside reverse transcriptase inhibitor has the attribute of interfering with in vivo viral replication. An NRTI operative in an inventive prophylactic process includes emtricitabine, lamivudine, zalcitabine, zidovudine, azidothymidine, didanosine, stavudine, abacavir; with the aforementioned specific NRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

An at least one nucleotide reverse transcriptase inhibitor (NRTI) present in an inventive composition to protect a primate from developing a self-replicating retroviral infection illustratively includes tenofovir, adefovir; 2',3'-dideoxy-3'-fluoroadenosine; 2',3'-dideoxy-3'-fluoroguanosine; 3'deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl guanosine with the aforementioned specific NtRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, and combinations thereof. Representative non-nucleoside reverse transcriptase inhibitors operative herein illustratively include delavirdine, efavirenz, nevirapine, and other diarylpyrimidine (DAPY) derivatives, Representative protease inhibitors operative herein illustratively include amprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, fosamprenavir calcium, ritonavir, atazanavir sulfate nelfinavir mesylate, and combinations thereof. An entry inhibitor operative herein as an optional active ingredient in an inventive composition illustratively includes enfuvirtide, Schering C (Schering Plough), S-1360 (Shionogi), and BMS806 (Bristol Myers Squibb).

The dose of individual active components of an inventive prophylactic composition is administered to create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure. It is appreciated that establishing a therapeutic concentration at the time of viral replication for a given NRTI, NtRTI or optional additional active agent in the target cells, includes factors for the therapeutic agent such as the route of administration, pharmacokinetics, absorption rate based on administration route, effects of food on oral absorption, in vivo distribution, metabolic pathways, elimination route, race, gender, and age of the subject, single dose incident side effects, long term administration side effects, and synergistic effects with co-administered active agents. Information related to these factors considered in dosing are available from the United States Food and Drug Administration http://www.fda.gov/oashi/aids/virals.html Preferably, NRTI and NtRTI prophylactic 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.

An inventive kit is provided that includes a 2-dose package of oral doses, such as tablets. In an exemplary embodiment of FDA approved NRTI and NtRTIs, each dose contains between 100 and 2500 milligrams (mg) of emtricitabine and between 100 and 2500 mg of TDF along with instructions to ingest the first dose approximately 1 to 8 hours prior to potential retroviral exposure and preferably about 2 hours therebefore, and a second dosage to be ingested 20 to 48 hours after potential retroviral exposure, preferably at about 22 hours thereafter. For an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF. A non-human primate dose according to the present invention is typically higher on a mg per kg animal body weight basis by a factor typically ranging from 2 to 10. Additional NRTIs, NtRTIs, NNRTIs, protease inhibitors or entry inhibitors are optionally provided in concert with either or both of these doses. The kit also includes instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the recipient (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. It is also appreciated that a carrier illustratively including a gel, jelly, cream, ointment, film, sponge, foam, suppository, vaginal ring or other delivery device is provided containing an NRTI such as emtricitabine, alone or in combination with an NtRTI such as tenofovir or TDF. The carrier is readily applied to mucosal tissue likely to be exposed to viral transmission as an added level of protection in concert with the oral doses.

An inventive kit is also provided that includes at least one NRTI and at least one NtRTI compounded as a gel, jelly, cream, ointment, film, sponge, foam, suppository, or applied to a vaginal ring or other like antiviral barrier. To prepare such a pharmaceutical compounded form, an effective amount of each of the active agents inclusive of at least one NRTI and NtRTI is combined in admixture with the pharmaceutically acceptable carrier or applied to a surface of the barrier. It is appreciated that the residence time of such a pharmaceutical composition is maintained at the site of administration through the inclusion of an optional bioadhesive that provides adhesion to mucosal tissue or the dermis. An inventive composition compounded for application to the dermis or mucosal tissue is provided along with instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the person (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. Optionally, a kit containing an oral dosage is combined with a composition compounded for application to the dermis, rectal mucosa or vaginal mucosa so as to assure a therapeutically effective combination of NRTI and NtRTI at the mucosal point of retroviral entry associated with sexual exposure, as well as a therapeutically effective serum circulating quantity of prophylactic antiretrovirals.

The present invention is further detailed with respect to the following non-limiting examples. These examples are intended to provide exemplary specific embodiments of the present invention and are not intended to limit the scope of the appended claims.

EXAMPLES

Example 1

Antiretroviral Drugs and Doses

A dose of 22 mg/kg of tenofovir disoproxil fumarate (TDF) is given orally and 20 mg/kg of emtricitabine (FTC) given orally or subcutaneously to one group of adult male rhesus macaques. The 22 mg/kg TDF dose resulted in an area-under the plasma concentration-time curve over a 24 h interval (AUC) of 4.49 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×hr/ml)[6]. Subcutaneous administration of FTC results in plasma FTC levels comparable to those achieved during oral administration, indicating a high FTC absorption in rhesus macaques.

Oral administration of FTC and TDF to macaques is by mixing the drug powders with peanut butter or fruit. Macaques are observed to ensure ingestion.

Example 2

Virus Inoculations

A chimeric envelope $SHIV_{SF162P3}$ isolate is used to inoculate the macaques. $SHIV_{SF162P3}$ is a construct that contains the tat, rev, and env coding regions of $HIV\text{-}1_{SF162}$ in a background of SIVmac239. This isolate was obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.[7,8] Virus exposures are performed 2 hours after drug treatment, and involved non-traumatic inoculation of 1 mL of $SHIV_{SF162P3}$ (10 $TCID_{50}$ or 7.5×10^6 viral RNA copies) into the rectal vault via a sterile gastric feeding tube.[9] Anesthetized macaques remained recumbent for at least 15 min after each intra-rectal inoculation.

Example 3

SHIV Viral Load Assay

Plasma RNA is quantified using a real-time PCR assay as previously described.[5] This assay has a sensitivity of detection of 50 RNA copies/ml or 10 copies of a pVp1 plasmid carrying the SIVmac239 RT gene. HIV-RNA is extracted from 1 mL of plasma using the NucliSens extraction method (bioMérieux). A known amount of virus particles (3×10^5) from an HIV-1 CM240 virus stock is added to each sample prior to extraction to control for the efficiency of extraction. Reverse transcription is performed using 10 microliters (μl) of extracted RNA and the 2-step TaqMan Gold reverse-transcriptase (RT)-PCR kit (Applied Biosystems) according to the manufacturer's instructions, PCR reactions are performed as described using an ABI 7000 Gene Detection System (Applied Biosystems). Virus loads are calculated from a standard curve generated with known amount of virus particles. All primers and probes used for SIVmac239 and HIV-1 CM240 have been reported elsewhere.[5] HIV-1 CM240 is obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.

Example 4

Detection of Genotypic Resistance to FTC and Tenofovir

Emergence of FTC and tenofovir resistance is monitored by sequence analysis of SIV RT (551 bp; amino acids 52 to 234) and by a more sensitive allele-specific real-time PCR method for the K65R and M184V mutations. Sequence analysis was done from plasma viruses using an RT-PCR procedure as previously described.[5] The Vector NTI program (Version 7, 2001) is used to analyze the data and to determine deduced amino-acid sequences. Detection of low frequency of K65R and M184V mutants in plasma by real-time PCR is performed as previously described.[10] These assays have a detection limit of 0.4% of K65R and 0.6% of M184V cloned sequences in a background of wild type plasmid.

Example 5

Virus-Specific Antibody Responses

Virus-specific serologic responses (IgG and IgM) are measured using a synthetic-peptide EIA (Genetic Systems HrV-1/HIV-2) assay.

Example 6

Statistical Methods

The exact log-rank test is used for a discrete-time survival analysis of the treatment and control groups, with use of the number of inoculations as the time variable. The Cox proportional hazards model is used to estimate the relative hazard ratio (HR). Percent protection is calculated from the HR value using the formula: (1-1/HR)×100. All statistical analyses for calculation of the efficacy of the different interventions are performed using SAS software (version 9.1; SAS Institute) and StatXact software (version 6.3; Cytel).

Example 7

Routine Dosing Experimental Design

Macaques are exposed rectally once weekly for up to 14 weeks to SHIV162p3 which contains an R5 tropic HIV-1 envelope that resembles naturally transmitted viruses. The SHIV162p3 challenge dose is 10 $TCID_{50}$ or 7.6×10^5 RNA copies which is similar to HIV-1 RNA levels in semen during acute infection in humans.[11] Virus exposures are terminated when a macaque became infected. FIG. **1** shows the study design and the interventions evaluated in each group of macaques. Three prophylactic drug treatments of increasing drug potency are each given once daily to a group of six macaques. Animals in Group 1 were treated subcutaneously with 20 mg/kg of FTC alone. Animals in Group 2 received orally a combination of FTC (20 mg/kg) and TDF (22 mg/kg). Animals in Group 3 had the most protective treatment with subcutaneous 20 mg/kg of FTC and a 22 mg/kg of tenofovir (PMPA). The rate of infection in each group is compared with that seen in 18 untreated control macaques (9 real time and 9 historical controls).

All treated macaques received the corresponding drugs 7 to 9 days prior to the first virus inoculation to achieve steady-state plasma levels. Treated animals that remained uninfected during the 14 challenges received 28 days of post-exposure prophylaxis after the last challenge. Protection was defined as absence of persistent viremia and seroconversion. Treated animals that became infected continued treatment for an average of 21 weeks (range=13 to 29) to monitor for plasma viremia and drug resistance development.

Example 8

Survival Curves

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/kg) is also provided for comparison. Untreated macaques are infected after a median of 2 rectal exposures (mean=4). The majority of the animals (13/18 or 72%) are infected during the first 4 challenges (median=2); 4 (22%) are infected between exposures 8 and 14 (mean=10), and only 1 (6%) remained uninfected after 14 exposures. The median 2 exposures for infection in controls suggests that an animal receiving prophylactic treatment and remaining uninfected after 14 virus challenges would have been protected against a median of 7 rounds of transmissions. Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed. All 6 macaques in Group 3 that received the most potent inventive composition remained uninfected demonstrating that full protection against repeated challenges is possible. Of the 6 macaques in Group 2, 4 were protected and only 2 (animal reference numbers AI-54 and AG-81) became infected at exposures 9 and 12. Compared to controls, infection in this group is reduced by 7.8-fold (Cox proportional hazard ratio [HR]=7.8, p=0.0075). Infection in both animals is significantly delayed compared to the untreated controls (p=0.0004). These 2 macaques became seropositive 2 weeks after the first detectable viral RNA in plasma and both were proviral DNA positive at weeks 10 and 12, respectively. Of the 6 macaques in Group 1 receiving FTC only, 2 remained protected after 14 exposures and 4 had the first detectable viral RNA at exposures 5 (AG-80), 10 (AG-46), 12 (AH-04), and 13 (AG-07), respectively. Survival analysis showed a statistically significant difference from untreated controls (p=0.004). Compared to controls, infection is reduced 3.8-fold macaques (Cox proportional hazard ratio [HR]=3.8, p=0.021). Infection in these 4 animals is also confirmed by PCR amplification of proviral DNA from PBMCs and by serology; antibody responses are detectable 3, 1, 2, and 6 weeks after the first detectable RNA, respectively. FIG. **2** also shows that the protection achieved with FTC alone was higher than that previously seen in 4 animals receiving TDF,[5] consistent with the slightly higher potency of FTC, although the difference was not statistically significant (p=0.5).

Example 9

Prophylactic Breakthrough Infections and Drug Resistance Emergence

Since the dynamics of breakthrough infections that occur during inventive prophylaxis and drug resistance emergence are unknown, the 6 infected animals from Groups 1 and 2 are followed under continued drug treatment. FIG. **3** compares the virus load kinetics in the 6 breakthrough infections with those in 12 untreated macaques that had sufficient follow-up samples. The mean peak viremia in the 6 treated macaques was 4.9 ± 0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9 ± 0.3 $\log_{10}$ RNA). FIG. **3** also shows that such differences in viremia were maintained up to week 11 as indicated by similar rate of virus load decline seen in the two groups of animals (-0.23 ± 0.02 $\log_{10}$/week in treated vs. -0.29 ± 0.02 $\log_{10}$/week in untreated controls). The individual virus load kinetics in the 6 breakthrough infections are shown in FIG. **4**. Three FTC (AG-80, AH-04, and AG-07) and one of the FTC/TDF (AG-81) failures had undetectable virus loads 3, 4, 7, and 11 weeks after the peak in viremia, respectively; viremia in these animals remained consistently low or undetectable for up to 20 weeks. In contrast, all 12 untreated macaques had detectable virus loads during a median follow-up period of 7 weeks (range=5-36 weeks). The arrow in FIG. **4** denotes the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in black full circles. Open circles are provided for data points not genotyped.

Drug resistance testing showed that wild type virus initiated all 6 breakthrough infections in Groups 1 and 2 reflecting residual virus replication in target cells not protected by drugs (FIG. **4**). Four animals had no evidence of drug resistance despite extended treatment (median=23 weeks). Only 2 animals had detectable M184V (AG-46, FTC-treated) or M184I (AI-54 FTC/TDF-treated) mutations associated with FTC resistance at week 4 and 10, respectively. The tenofovir-associated K65R mutation is not detected in the 2 Group 2 animals receiving FTC/TDF. FIG. **4** also shows that the 2 macaques that selected M184V/I had the highest peak viremias. Without intending to be bound to a particular theory, it is hypothesized that more virus replication in these animals may have facilitated drug resistance selection. Reductions in acute viremia are proposed to contribute at a population level to a decrease in virus transmissibility.

Example 10

Single Dosing

The process of Example 7 is repeated in Group 3 with drugs only being administered 2 hours prior to and 22 hours subsequent to each inoculation. The resultant survival curves are comparable to those detailed in Example 8.

Example 11

Single Dosing with Suppository

A group of 6 macaques received the drug treatment of Group 3 per Example 7 in the form of a gel inserted rectally containing 300 mg of tenofovir and 300 mg lamuvidine (3-TC) 1 hour before viral inoculation with observation to assure that the suppository is not voided. The gel is formed by compounding tenofovir and 3-TC in 2% by weight hydroxyethyl cellulose (HEC)-based gel in both a vaginal formulation (pH 4.5) and rectal formulation (pH 6.5) containing (w/v) 3% tenofovir, and 3% 3-TC. The gels are stable at room temperature for at least five months with no loss in activity; and gels retained full activity at both pH 4.5 and pH 6.5 at levels equivalent to those observed for tenofovir and 3-TC preparations in water. Using an MT4/MTT phenotypic assay, all gels were tested for activity against wild-type HIV-1_{HXB2}, and resistant HIV-1 viruses containing the K65R or M184V mutations. No significant cytotoxicity is seen in the cervical explant model.

Viral protection of the macaques is maintained throughout the study.

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Patent documents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These documents and publications are incorporated herein by reference to the same extent as if each individual document or publication was specifically and individually incorporated herein by reference.

The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the invention.

The invention claimed is:

1. 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.

2. The process of claim **1** wherein selecting a primate host comprises selecting an adult human not infected with the immunodeficiency retrovirus.

3. The process of claim **2** wherein the adult primate host is a male adult primate host.

4. The process of claim **1** wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir disoproxil fumarate, are administered orally directly to the human in a combined single dosage formulation.

5. The process of claim **1** wherein the immunodeficiency retrovirus is a human immunodeficiency virus.

6. The process of claim **5** wherein the human immunodeficiency virus (HIV) is HIV-1.

7. The process of claim 1 wherein the combination is administered as preexposure prophylactic treatment prior to rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus.

8. The process of claim 1 comprising administering 200 milligrams (mg) of emtricitabine and 300 mg of tenofivir disoproxil fumarate to a human host.

9. The process of claim 1 wherein the combination is administered daily for several days, weeks or months.

10. The process of claim 9 wherein 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.

11. The process of claim 1 wherein administration of the combination results in an absence of persistent viremia and seroconversion of the primate host.

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir ester;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered orally.

13. The process of claim 12 wherein the combination is administered prior to a potential exposure of the primate host to the human immunodeficiency retrovirus.

14. The process of claim 12 wherein the combination is compounded into a single combination formulation suitable for oral administration.

15. The process of claim 12 wherein an inhibition of infection in the host is determined by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.

16. The process of claim 12 wherein the combination is administered following potential exposure of the primate host to the human immunodeficiency retrovirus.

17. The process of claim 16 wherein the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.

18. The process of claim 12 wherein the tenofovir ester is tenofovir disoproxil fumarate.

* * * * *

US009579333B2

(12) United States Patent

Heneine et al.

(10) Patent No.: US 9,579,333 B2
(45) Date of Patent: *Feb. 28, 2017

(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYALXIS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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A61K 31/675 (2006.01)
A61K 31/505 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61K 31/683*** (2013.01); ***A61K 31/513*** (2013.01); ***A61K 31/675*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC A61K 31/7072; A61K 31/675
(Continued)

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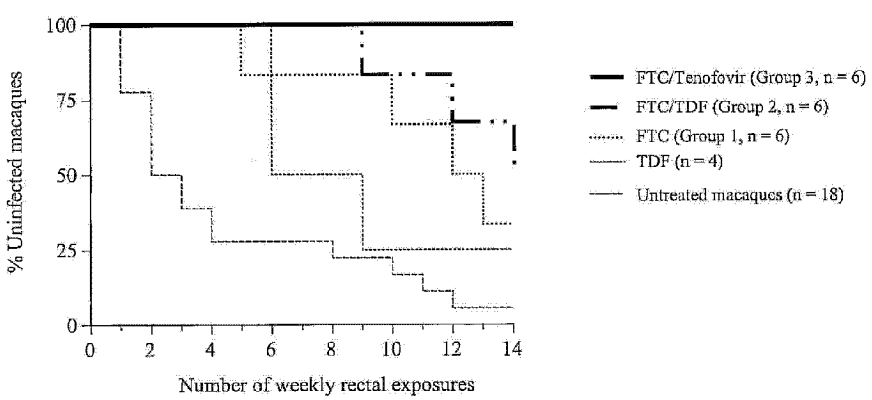
(57) **ABSTRACT**

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose within 24 hours of the exposure. A regime of regular daily doses is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for
(Continued)



controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection the detailed combination prior to sexual exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

17 Claims, 4 Drawing Sheets

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A61K 31/7072	(2006.01)
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CPC ***A61K 31/7072*** (2013.01); ***A61K 45/06*** (2013.01); *A61K 9/0034* (2013.01)

(58) **Field of Classification Search**
USPC 514/81, 274
See application file for complete search history.

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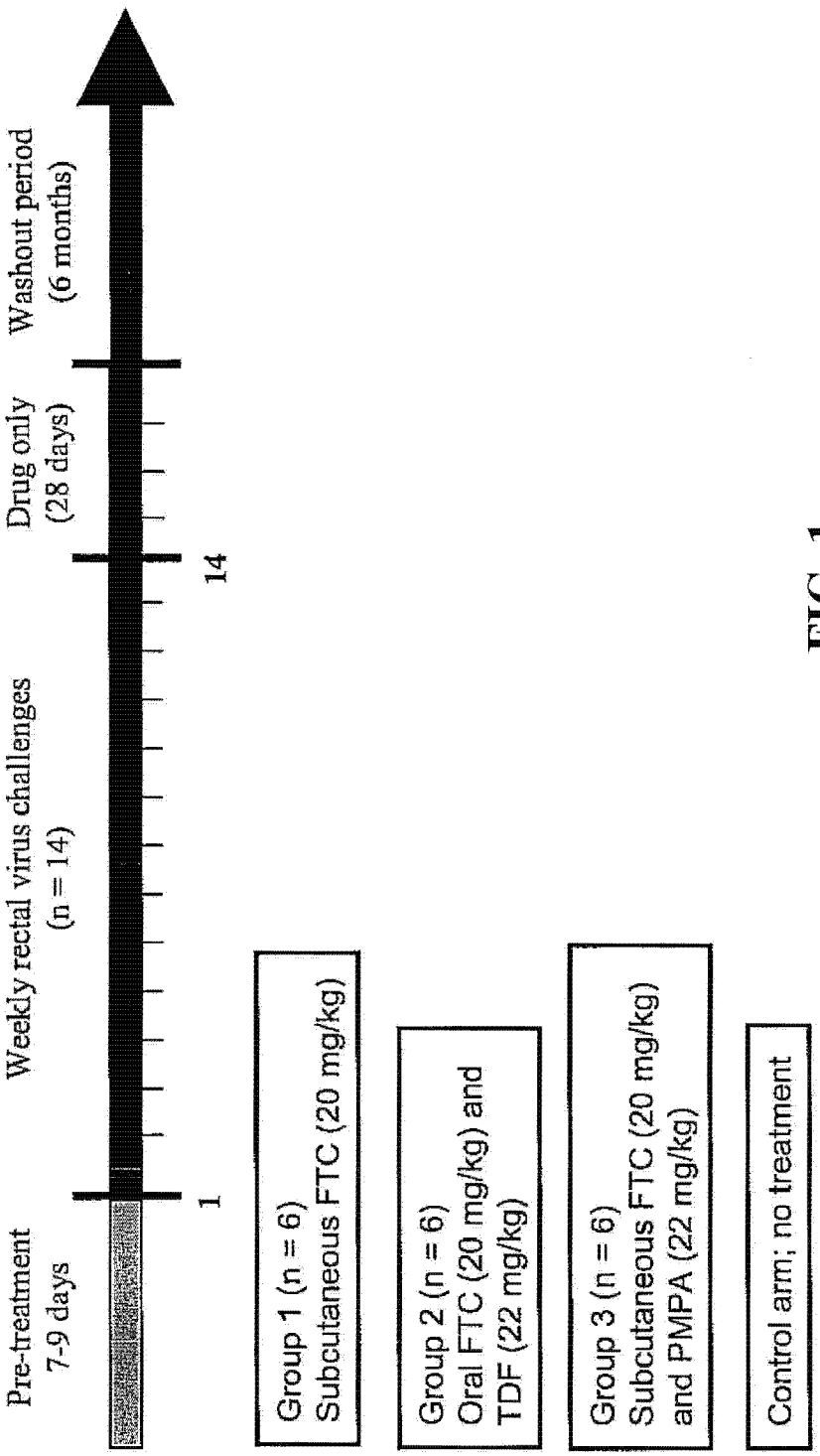

FIG. 1

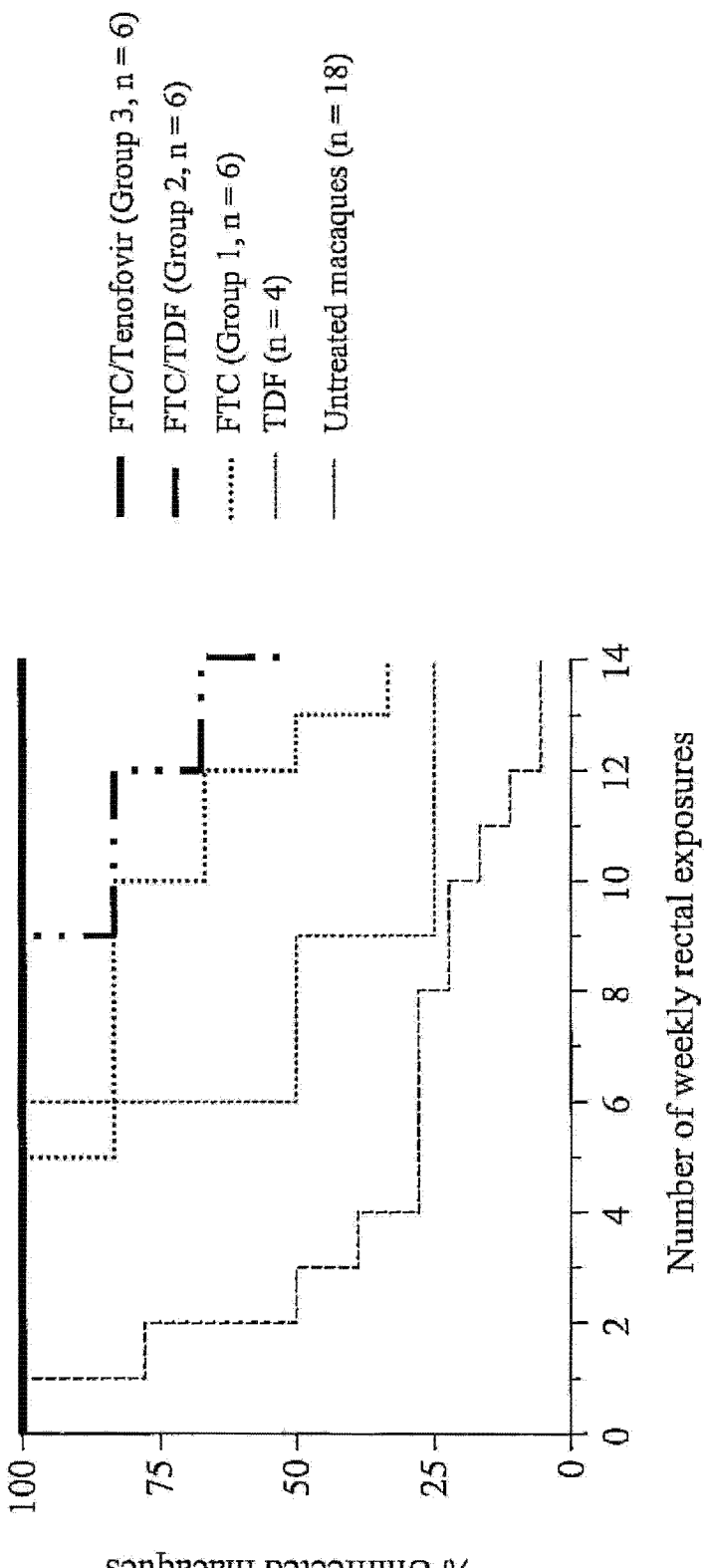
FTC/Tenofovir (Group 3, n = 6)
FTC/TDF (Group 2, n = 6)
FTC (Group 1, n = 6)
TDF (n = 4)
Untreated macaques (n = 18)
% Uninfected macaques
100
75
50
25
0
0
2
4
6
8
10
12
14
Number of weekly rectal exposures

FIG. 2

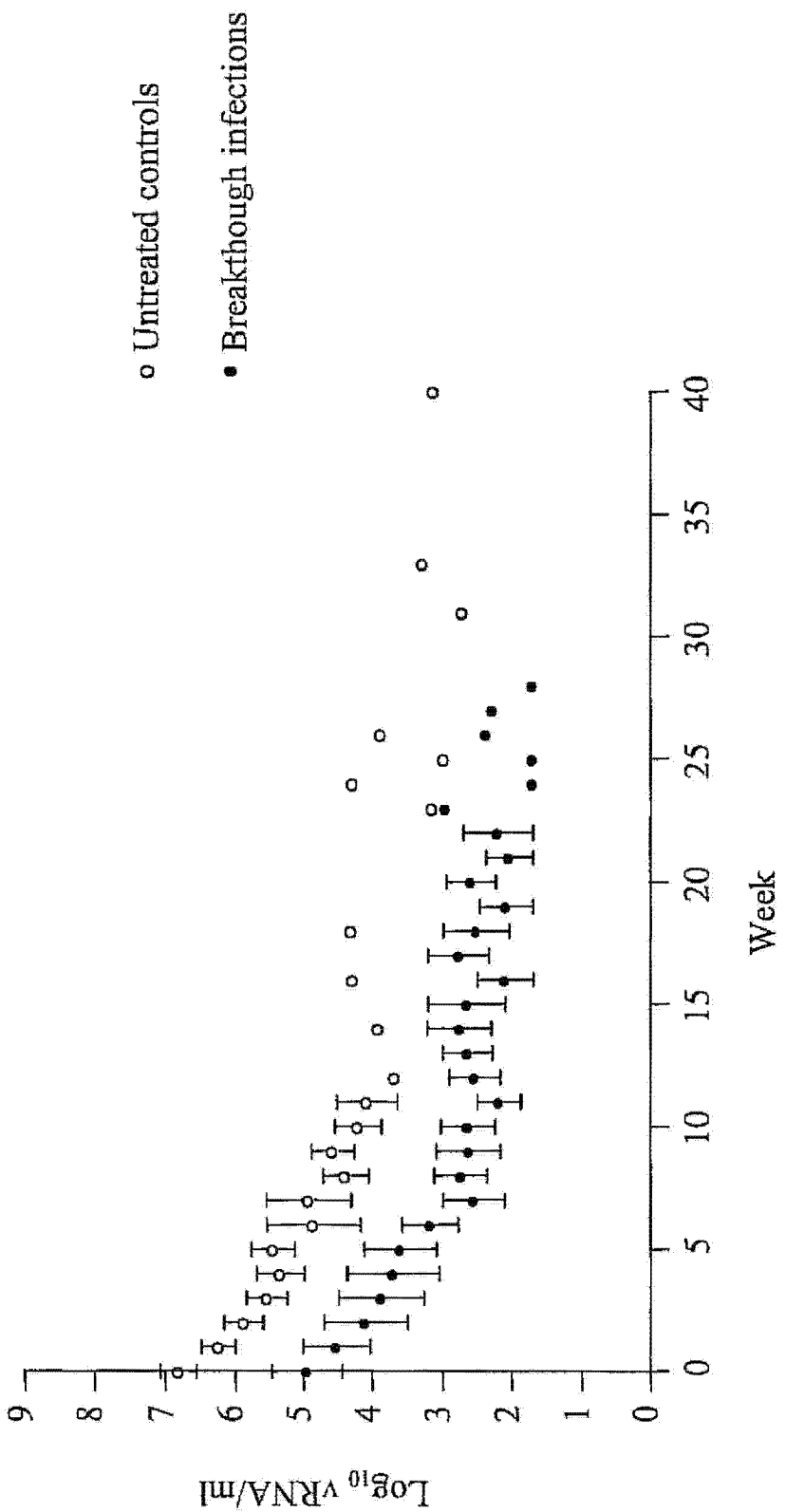
o Untreated controls
• Breakthough infections
Log10 vRNA/ml
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30
35
40
Week

FIG. 3

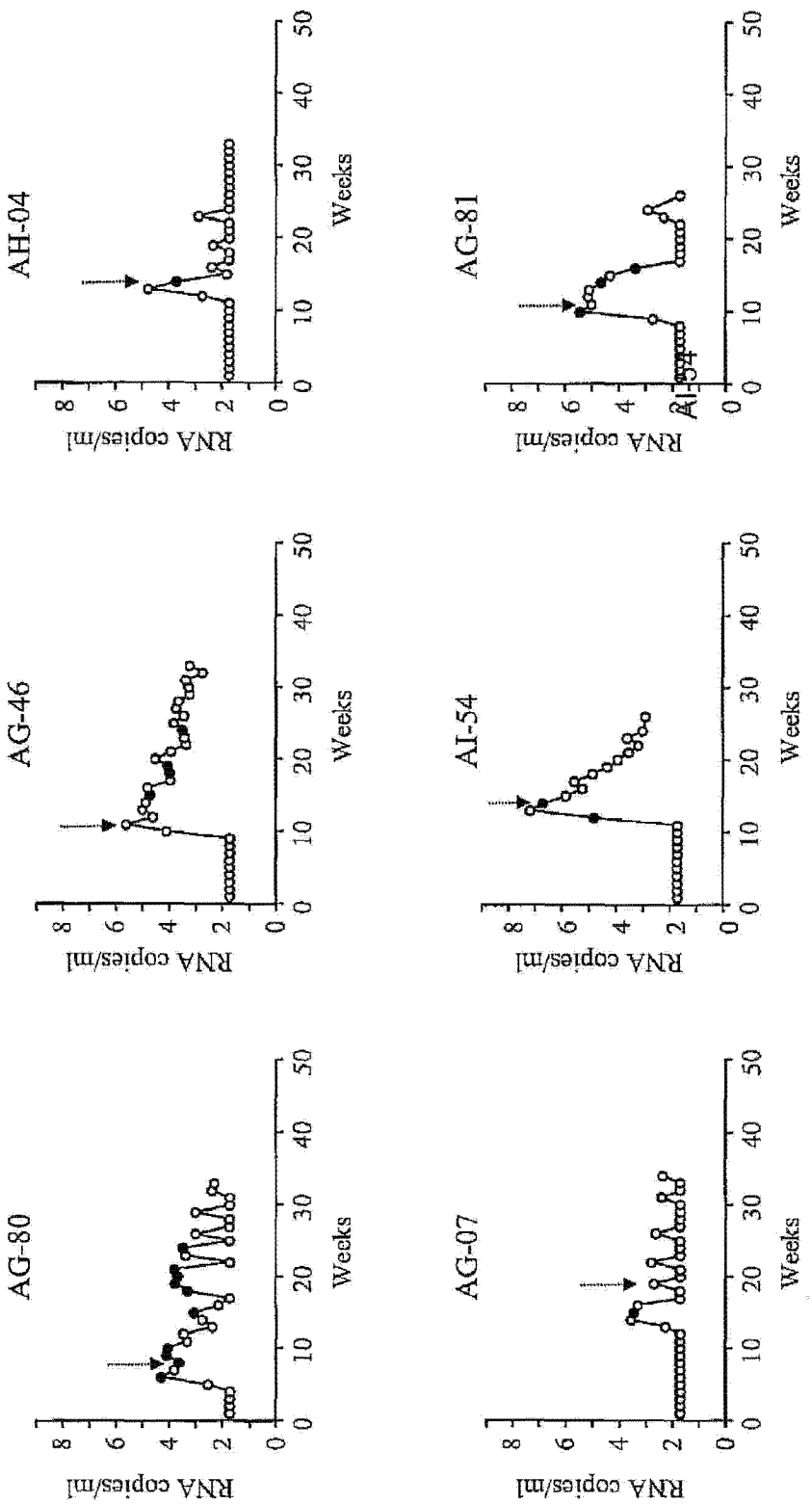
AH-04
AG-81
AG-46
AI-54
AG-80
AG-07
RNA copies/ml
Weeks
0
2
4
6
8
0
10
20
30
40
50

FIG. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYALXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. patent application Ser. No. 11/669,547, filed on Jan. 31, 2007, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on Feb. 3, 2006. Both of the prior applications are incorporated herein by reference in their entirety.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

The present invention in general relates to a process for inhibiting initial infection by a retrovirus such as human immunodeficiency virus (HIV) and in particular to a combination of a nucleoside reverse transcriptase inhibitor (NRTI) and a nucleotide reverse transcriptase inhibitor (NtRTI) capable of preventing self-replicating retroviral infection, even in response to multiple viral challenges.

BACKGROUND OF THE INVENTION

Despite the fact that significant progress has been made slowing the advancement of the symptoms of AIDS associated with HIV infection, in the absence of an effective vaccine, HIV continues to spread globally. The spread of HIV persists in part because an infected individual remains a potential source of injection. It is clear that current treatment of monitoring viral titer and in response to a titer exceeding a preselected threshold commencing treatment with highly active antiretroviral therapy (HAART) has not prevented new infections.

An attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment. As HIV and, in particular HIV-1, often begins with a comparatively small population of retroviral particles being transmitted to a new host and within a few days self-replicating into a retroviral titer detectable in host blood serum. 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.

Previous attempts at pre-exposure prophylaxis have met with limited success. Prophylactic activity has been demonstrated with the NtRTI, tenofovir in monkey models challenged with simian immunodeficiency virus (SIV).[1-3] Unfortunately, oral daily dosing and pre-exposure prophylaxis with tenofovir at a dose equivalent to that used in humans proved to only be partially protective against rectal SHIV transmission.[4]

HAART therapy involves the administration of a combination including at least three active compounds classified by the mode of operation as an NRTI, an NtRTIs, a non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitor, and an entry inhibitor. While HAART is effective in lowering retroviral titer in a host, concerns remain as to the long term toxicity and the retained potential to infect others. It is also unknown if initiating HAART therapy in a pre-exposure prophylactic regimen would be efficacious. As a result, society remains devoid of a pre-exposure prophylactic regimen to prevent an individual from developing self-propagating retrovirus infection subsequent to initial exposure.

Thus, there exists a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population. There also exists a need for a chemoprophylactic composition formulated with a vehicle amenable to user compliance.

SUMMARY OF THE INVENTION

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose prior to the exposure. A regime of multiple temporally spaced doses prior to retroviral exposure is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection a combination of a pharmaceutically effective nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

A kit is also provided that includes at least one combination dose of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor sufficient to protect a primate host from developing a self-replicating retroviral infection along with instructions for the administration of the at least one dose one prior to and optionally one additional dose subsequent to a potential exposure to an immunodeficiency retrovirus along with dosing modifications associated with subject characteristics and behaviors to further reduce the risk of contracting a self-replicating immunodeficiency retrovirus infection.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic depicting one study of the present invention for 4 groups of macaques in which all treated macaques received known antiretroviral medications 7 to 9 days prior to the first virus inoculation and continuing throughout the study with treated animals that remained uninfected throughout the 14 viral challenges receiving 28 additional days of post-exposure prophylactics.

FIG. **2** is a survival curve graph for macaque Groups 1-4 per FIG. **1**, as well as for animals receiving only tenofovir disoproxil fumarate (TDF).

FIG. **3** is a graph depicting a plot of viremia as a function of time for untreated controls (○) and breakthrough infections (●) where each point represents a mean viremia observed, 0 time indicates peak plasma virus load observed in a given animal where the arrow bars denote standard error of the mean (SEM).

FIG. **4** depicts plots of infection dynamics as a function of time during the study per FIG. **1** with plots for animals coded as AG-80, AG-46, AH-04 and AG-07 corresponding to

emtricitabine (FTC) treatment alone, or FTC plus TDF treatment (AI-54 and AG-81). The arrow indicates the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in as black full circles. Open circles indicate the time points where no genotype was undertaken.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention has utility in protecting a primate host from self-propagating immunodeficiency virus infection. The use of a combination of antiretroviral agents as a prophylactic dosing regime is also provided for the manufacture of a medicament is provided for protection against a human immunodeficiency virus infection developing to a level of self-replicating infection. Retroviral transmission through most routes entails a new primate host receiving a small number of viral particles. Common routes of retrovirus transmission illustratively include sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, blood transfusions, birth canal exposure, breastfeeding, and transplacental contact between individuals. Through the administration of at least one nucleoside reverse transcriptase inhibitor (NRTI) and at least one nucleotide reverse transcriptase inhibitor (NtRTI) prior to a retrovirus exposure protection is provided against development of a self-replicating retroviral infection. As the aforementioned exposure routes are characterized by a small number of retrovirus particles being transferred to the new primate host, this initial phase of infection represents a window of opportunity to protect a host from infection. The inventive chemoprophylactic treatment is provided through a dosing regimen. A dosing regimen according to the present invention that provides retroviral protection to a host primate includes at least one single dose administered prior to initial retroviral exposure. An inventive dosing regimen also includes a course of multiple doses administered in advance of exposure to maintain a therapeutic level of NRTI and NtRTI agents in the primate host. The timing of the at least one does prior to retroviral exposure is dictated by the pharmacokinetics of the NRTI and NtRTI components to assure the presence of a therapeutically effective amount of inventive composition for at least 20 hours subsequent to the exposure to the communicated small retroviral particle population. Multiple doses are administered according to the present invention at regular time intervals and amounts such as for example like formulated daily doses for a period of several days, weeks, or months; or are administered in advance of a likely exposure as a cluster of doses, with the amount of NRTI and NtRTI components in each dose being independent of the of amount of NRTI and NtRTI in other doses within the cluster. While most oral, topical, and parenteral existing versions of NRTIs and NtRTIs are fully absorbed and therapeutically active within 1 to 8 hours, it is appreciated that subcutaneous implants and long acting timed release formulations allow for a single dose to sustain therapeutically effective amounts of an inventive prophylactic composition for several days, weeks, or even months. Representative of sustained release compositions and implants are provided in the U.S. Pat. Nos. 4,122,129; 4,927,687; 4,996,047; 5,169,642; and 5,656,296.

The combination of NRTI and NtRTI compounds administered prophylactically according to the present invention are shown to provide a dose-dependent inhibition of HIV self-replicating infection and a therapeutically effective dosing primate host protection against self-replicating HIV infection is provided, even in response to multiple viral challenges. While the present invention is largely detailed with respect to HIV-1 as a prototypical infectious and pathogenic retrovirus, it is appreciated that other retroviruses owing to reliance on reverse transcription for replication are also protected against in a primate host according to the present invention.

As used herein, "protection" as used in the context of a host primate response to an immunodeficiency virus challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.

As used herein, the term "retrovirus" is inclusive of any virus that utilizes reverse transcriptase in the viral replication cycle and therefore is susceptible to the antiviral activity of nucleoside or nucleotide analogs specifically inclusive of HIV (HIV-1 and HIV-2), HTLV-1, HTLV-2, HTLV-3, HTLV-4, and SIV. Also encompassed are viruses such as HBV that although not technically classified as retroviruses nonetheless utilize a reverse transcriptase and are therefore susceptible to the antiviral activity of nucleoside and/or nucleotide analogs.

As used herein a "primate host" is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Non-human primates are appreciated to themselves be susceptible to infection by retroviruses and in particular immunodeficiency viruses and represent well-established animal models as to human response with an appreciation that physiological differences often require different doses in milligrams per kilogram for a nonhuman primate animal model relative to a human.

The compositions of the present invention include administration in combination of an NRTI and NtRTI and are readily compounded by pharmaceutical composition with conventional pharmaceutically acceptable carriers or diluents. Additionally, pharmaceutically acceptable derivatives and prodrugs of active NRTIs and NtRTIs operative in the present invention include salts such as alkali metal salts; esters such as acetate, butyrate, octinoate, palmitate, chlorobenzoates, benzoates, C_1-C_6 benzoates, succinates, and mesylate; salts of such esters; and nitrile oxides. It is appreciated that other analogs of pharmaceutically active NRTIs or NtRTIs that provide within a primate host an active antiviral metabolite residue are also suitable as part of an inventive composition. A pharmaceutically acceptable carrier or diluent includes agents that are compatible with other ingredients of a dosage and not injurious to a primate host. The identity and process for compounding a combination of at least one NRTI and at least one NtRTI into a dosage form suitable for delivery by a route with administration by oral, rectal, topical, vaginal or parenteral routes of administration are provided in Remington's Science and Practice of Pharmacology, 20th Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

As used herein the term "prodrug" is defined to include a compound that when administered to a primate host generates an active NRTI or NtRTI as a result of spontaneous reaction under physiological conditions, enzymatic catalysis, metabolic clearance, or combinations thereof. An exemplary NtRTI prodrug currently FDA approved for HAART use is tenofovir disoproxil fumarate (TDF) and is detailed in U.S. Pat. No. 5,935,946.

The present invention provides an alternative to conventional retroviral therapy using HAART, in response to self-propagating HIV infection by protecting a primate host

against the establishment of self-replicating retroviral infection that provides an indication for such therapy. Through prophylactic prior dosing with an inventive combination including at least one NRTI and one NtRTI, replication of the comparatively low number of viral particles received by a host primate is prevented.

To achieve protection against a primate host developing a retroviral self-replicating infection, at least one dosage of an NRTI and NtRTI is administered to the primate host prior to exposure to the retrovirus. Preferably, the at least one NRTI and at least one NtRTI are administered concurrently. More preferably, the combination of reverse transcriptase inhibitors is compounded into a single formulation.

The process of the present invention demonstrates protection against retroviral self-replicating infection through administration of even a single dosage administered prior to the retroviral exposure. Owing to the known pK rates of specific NRTIs and NtRTIs, a single dosage is administered to assure a therapeutically effective amount of NRTI and NtRTI persist in the primate host for a time of more than 12 hours after viral challenge. With conventional NRTI and NtRTI formulations, currently approved for HAART, preferably an inventive dose is administered within 12 hours prior to retroviral exposure and still more preferably often within 2 hours prior to retroviral exposure. The practice of the inventive process involving the administration of a single dosage in the hours proceeding a likely retroviral exposure is particularly advantageous in assuring compliant dosing in a human and also avoids side effects associated with a regular dosing regime and is particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure. Preferably, an additional dose or doses of a combination of at least one NRTI and at least one NtRTIs is provided subsequent to the retroviral exposure event to assure adequate antiviral reverse transcriptase inhibitor concentration during and immediately subsequent to retroviral infection of the host founder cell population so as to preclude retroviral self-replication to assure NRTI and NtRTI incorporation into a replicating virus genome. Preferably, a dose of an inventive composition taken after retroviral exposure is administered within 24 hours subsequent to the exposure, and more preferably within 12 hours subsequent to the exposure.

Alternatively, an individual routinely subjected to retroviral exposure can be protected against the development of a self-replicating retroviral infection through administration of regular prophylactic doses of an inventive combination. As a result, an epidemiological advantage exists in controlling the outbreak and spread of a retrovirus within a population is provided through offering routine doses of an inventive composition prophylactically to high-risk persons such as sex workers and a short course prophylactic inventive composition to uninfected sex trade clientele.

It is appreciated that hybrid dosing regimes of an inventive composition are also operative herein and include multiple doses prior to retroviral exposure with multiple doses not being administered for a duration or with sufficient periodicity to arise to the level of a routine prophylactic regime.

The at least one nucleoside reverse transcriptase inhibitor has the attribute of interfering with in vivo viral replication. An NRTI operative in an inventive prophylactic process includes emtricitabine, lamivudine, zalcitabine, zidovudine, azidothymidine, didanosine, stavudine, abacavir; with the aforementioned specific NRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

An at least one nucleotide reverse transcriptase inhibitor (NRTI) present in an inventive composition to protect a primate from developing a self-replicating retroviral infection illustratively includes tenofovir, adefovir; 2',3'-dideoxy-3'-fluoroadenisine; 2',3'-dideoxy-3'-fluoroguanasine; 3'deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine with the aforementioned specific NtRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, and combinations thereof. Representative non-nucleoside reverse transcriptase inhibitors operative herein illustratively include delavirdine, efavirenz, nevirapine, and other diarylpyrimidine (DAPY) derivatives. Representative protease inhibitors operative herein illustratively include amprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, fosamprenavir calcium, ritonavir, atazanavir sulfate nelfinavir mesylate, and combinations thereof. An entry inhibitor operative herein as an optional active ingredient in an inventive composition illustratively includes enfuvirtide, Schering C (Schering Plough), S-1360 (Shionogi), and BMS806 (Bristol Myers Squibb).

The dose of individual active components of an inventive prophylactic composition is administered to create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure. It is appreciated that establishing a therapeutic concentration at the time of viral replication for a given NRTI, NtRTI or optional additional active agent in the target cells, includes factors for the therapeutic agent such as the route of administration, pharmacokinetics, absorption rate based on administration route, effects of food on oral absorption, in vivo distribution, metabolic pathways, elimination route, race, gender, and age of the subject, single dose incident side effects, long term administration side effects, and synergistic effects with co-administered active agents. Information related to these factors considered in dosing are available from the United States Food and Drug Administration (http://www.fda.gov/oashi/aids/virals.html) Preferably, NRTI and NtRTI prophylactic 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.

An inventive kit is provided that includes a 2-dose package of oral doses, such as tablets. In an exemplary embodiment of FDA approved NRTI and NtRTIs, each dose contains between 100 and 2500 milligrams (mg) of emtricitabine and between 100 and 2500 mg of TDF along with instructions to ingest the first dose approximately 1 to 8 hours prior to potential retroviral exposure and preferably about 2 hours there before, and a second dosage to be ingested 20 to 48 hours after potential retroviral exposure, preferably at about 22 hours thereafter. For an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF. A non-human primate dose according to the present invention is typically higher on a mg per kg animal body weight basis by a factor typically ranging from 2 to 10. Additional NRTIs, NtRTIs, NNRTIs, protease inhibitors or entry inhibitors are optionally provided in concert with either or both of these doses. The kit also includes instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the recipient (synonymously described herein as a human primate host) can undertake to

reduce the risk of retrovirus exposure and initial infection. It is also appreciated that a carrier illustratively including a gel, jelly, cream, ointment, film, sponge, foam, suppository, vaginal ring or other delivery device is provided containing an NRTI such as emtricitabine, alone or in combination with an NtRTI such as tenofovir or TDF. The carrier is readily applied to mucosal tissue likely to be exposed to viral transmission as an added level of protection in concert with the oral doses.

An inventive kit is also provided that includes at least one NRTI and at least one NtRTI compounded as a gel, jelly, cream, ointment, film, sponge, foam, suppository, or applied to a vaginal ring or other like antiviral barrier. To prepare such a pharmaceutical compounded form, an effective amount of each of the active agents inclusive of at least one NRTI and NtRTI is combined in admixture with the pharmaceutically acceptable carrier or applied to a surface of the barrier. It is appreciated that the residence time of such a pharmaceutical composition is maintained at the site of administration through the inclusion of an optional bioadhesive that provides adhesion to mucosal tissue or the dermis. An inventive composition compounded for application to the dermis or mucosal tissue is provided along with instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the person (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. Optionally, a kit containing an oral dosage is combined with a composition compounded for application to the dermis, rectal mucosa or vaginal mucosa so as to assure a therapeutically effective combination of NRTI and NtRTI at the mucosal point of retroviral entry associated with sexual exposure, as well as a therapeutically effective serum circulating quantity of prophylactic antiretrovirals.

The present invention is further detailed with respect to the following non-limiting examples. These examples are intended to provide exemplary specific embodiments of the present invention and are not intended to limit the scope of the appended claims.

EXAMPLES

Example 1

Antiretroviral Drugs and Doses

A dose of 22 mg/kg of tenofovir disoproxil fumarate (TDF) is given orally and 20 mg/kg of emtricitabine (FTC) given orally or subcutaneously to one group of adult male rhesus macaques. The 22 mg/kg TDF dose resulted in an area-under the plasma concentration-time curve over a 24 h interval (AUC) of 4.49 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×hr/ml)[6]. Subcutaneous administration of FTC results in plasma FTC levels comparable to those achieved during oral administration, indicating a high FTC absorption in rhesus macaques.

Oral administration of FTC and TDF to macaques is by mixing the drug powders with peanut butter or fruit. Macaques are observed to ensure ingestion.

Example 2

Virus Inoculations

A chimeric envelope $SHIV_{SF162P3}$ isolate is used to inoculate the macaques. $SHIV_{SF162P3}$ is a construct that contains the tat, rev, and env coding regions of $HIV\text{-}1_{SF162}$ in a background of SIVmac239. This isolate was obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.[7,8] Virus exposures are performed 2 hours after drug treatment, and involved non-traumatic inoculation of 1 mL of $SHIV_{SF162P3}$ (10 $TCID_{50}$ or 7.5×10^6 viral RNA copies) into the rectal vault via a sterile gastric feeding tube.[9] Anesthetized macaques remained recumbent for at least 15 min after each intrarectal inoculation.

Example 3

SHIV Viral Load Assay

Plasma RNA is quantified using a real-time PCR assay as previously described.[5] This assay has a sensitivity of detection of 50 RNA copies/ml or 10 copies of a pVp1 plasmid carrying the SIVmac239 RT gene. HIV-1 RNA is extracted from 1 mL of plasma using the NucliSens extraction method (bioMérieux). A known amount of virus particles (3×10^5) from an HIV-1 CM240 virus stock is added to each sample prior to extraction to control for the efficiency of extraction. Reverse transcription is performed using 10 microliters (μl) of extracted RNA and the 2-step TaqMan Gold reverse-transcriptase (RT)-PCR kit (Applied Biosystems) according to the manufacturer's instructions. PCR reactions are performed as described using an ABI 7000 Gene Detection System (Applied Biosystems). Virus loads are calculated from a standard curve generated with known amount of virus particles. All primers and probes used for SIVmac239 and HIV-1 CM240 have been reported elsewhere.[5] HIV-1 CM240 is obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.

Example 4

Detection of Genotypic Resistance to FTC and Tenofovir

Emergence of FTC and tenofovir resistance is monitored by sequence analysis of SIV RT (551 bp; amino acids 52 to 234) and by a more sensitive allele-specific real-time PCR method for the K65R and M184V mutations. Sequence analysis was done from plasma viruses using an RT-PCR procedure as previously described.[5] The Vector NTI program (Version 7, 2001) is used to analyze the data and to determine deduced amino-acid sequences. Detection of low frequency of K65R and M184V mutants in plasma by real-time PCR is performed as previously described.[10] These assays have a detection limit of 0.4% of K65R and 0.6% of M184V cloned sequences in a background of wild type plasmid.

Example 5

Virus-Specific Antibody Responses

Virus-specific serologic responses (IgG and IgM) are measured using a synthetic-peptide EIA (Genetic Systems HIV-1/HIV-2) assay.

Example 6

Statistical Methods

The exact log-rank test is used for a discrete-time survival analysis of the treatment and control groups, with use of the

number of inoculations as the time variable. The Cox proportional hazards model is used to estimate the relative hazard ratio (HR). Percent protection is calculated from the HR value using the formula: (1−1/HR)×100. All statistical analyses for calculation of the efficacy of the different interventions are performed using SAS software (version 9.1; SAS Institute) and StatXact software (version 6.3; Cytel).

Example 7

Routine Dosing Experimental Design

Macaques are exposed rectally once weekly for up to 14 weeks to SHIV162p3 which contains an R5 tropic HIV-1 envelope that resembles naturally transmitted viruses. The SHIV162p3 challenge dose is 10 $TCID_{50}$ or 7.6×10^5 RNA copies which is similar to HIV-1 RNA levels in semen during acute infection in humans.[11] Virus exposures are terminated when a macaque became infected. FIG. **1** shows the study design and the interventions evaluated in each group of macaques. Three prophylactic drug treatments of increasing drug potency are each given once daily to a group of six macaques. Animals in Group 1 were treated subcutaneously with 20 mg/kg of FTC alone. Animals in Group 2 received orally a combination of FTC (20 mg/kg) and TDF (22 mg/kg). Animals in Group 3 had the most protective treatment with subcutaneous 20 mg/kg of FTC and a 22 mg/kg of tenofovir (PMPA). The rate of infection in each group is compared with that seen in 18 untreated control macaques (9 real time and 9 historical controls).

All treated macaques received the corresponding drugs 7 to 9 days prior to the first virus inoculation to achieve steady-state plasma levels. Treated animals that remained uninfected during the 14 challenges received 28 days of post-exposure prophylaxis after the last challenge. Protection was defined as absence of persistent viremia and seroconversion. Treated animals that became infected continued treatment for an average of 21 weeks (range=13 to 29) to monitor for plasma viremia and drug resistance development.

Example 8

Survival Curves

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/kg) is also provided for comparison. Untreated macaques are infected after a median of 2 rectal exposures (mean=4). The majority of the animals (13/18 or 72%) are infected during the first 4 challenges (median=2); 4 (22%) are infected between exposures 8 and 14 (mean=10), and only 1 (6%) remained uninfected after 14 exposures. The median 2 exposures for infection in controls suggests that an animal receiving prophylactic treatment and remaining uninfected after 14 virus challenges would have been protected against a median of 7 rounds of transmissions. Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed. All 6 macaques in Group 3 that received the most potent inventive composition remained uninfected demonstrating that full protection against repeated challenges is possible. Of the 6 macaques in Group 2, 4 were protected and only 2 (animal reference numbers AI-54 and AG-81) became infected at exposures 9 and 12. Compared to controls, infection in this group is reduced by 7.8-fold (Cox proportional hazard ratio [HR]=7.8, p=0.0075). Infection in both animals is significantly delayed compared to the untreated controls (p=0.0004). These 2 macaques became seropositive 2 weeks after the first detectable viral RNA in plasma and both were proviral DNA positive at weeks 10 and 12, respectively. Of the 6 macaques in Group 1 receiving FTC only, 2 remained protected after 14 exposures and 4 had the first detectable viral RNA at exposures 5 (AG-80), 10 (AG-46), 12 (AH-04), and 13 (AG-07), respectively. Survival analysis showed a statistically significant difference from untreated controls (p=0.004). Compared to controls, infection is reduced 3.8-fold macaques (Cox proportional hazard ratio [HR]=3.8, p=0.021). Infection in these 4 animals is also confirmed by PCR amplification of proviral DNA from PBMCs and by serology; antibody responses are detectable 3, 1, 2, and 6 weeks after the first detectable RNA, respectively. FIG. **2** also shows that the protection achieved with FTC alone was higher than that previously seen in 4 animals receiving TDF,[5] consistent with the slightly higher potency of FTC, although the difference was not statistically significant (p=0.5).

Example 9

Prophylactic Breakthrough Infections and Drug Resistance Emergence

Since the dynamics of breakthrough infections that occur during inventive prophylaxis and drug resistance emergence are unknown, the 6 infected animals from Groups 1 and 2 are followed under continued drug treatment. FIG. **3** compares the virus load kinetics in the 6 breakthrough infections with those in 12 untreated macaques that had sufficient follow-up samples. The mean peak viremia in the 6 treated macaques was 4.9±0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9±0.3 $\log_{10}$ RNA). FIG. **3** also shows that such differences in viremia were maintained up to week 11 as indicated by similar rate of virus load decline seen in the two groups of animals (−0.23±0.02 $\log_{10}$/week in treated vs. −0.29±0.02 $\log_{10}$/week in untreated controls). The individual virus load kinetics in the 6 breakthrough infections are shown in FIG. **4**. Three FTC (AG-80, AH-04, and AG-07) and one of the FTC/TDF (AG-81) failures had undetectable virus loads 3, 4, 7, and 11 weeks after the peak in viremia, respectively; viremia in these animals remained consistently low or undetectable for up to 20 weeks. In contrast, all 12 untreated macaques had detectable virus loads during a median follow-up period of 7 weeks (range=5-36 weeks). The arrow in FIG. **4** denotes the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in black full circles. Open circles are provided for data points not genotyped.

Drug resistance testing showed that wild type virus initiated all 6 breakthrough infections in Groups 1 and 2 reflecting residual virus replication in target cells not protected by drugs (FIG. **4**). Four animals had no evidence of drug resistance despite extended treatment (median=23 weeks). Only 2 animals had detectable M184V (AG-46, FTC-treated) or M1841 (AI-54 FTC/TDF-treated) mutations associated with FTC resistance at week 4 and 10, respectively. The tenofovir-associated K65R mutation is not detected in the 2 Group 2 animals receiving FTC/TDF. FIG. **4** also shows that the 2 macaques that selected M184V/I had the highest peak viremias. Without intending to be bound to a particular theory, it is hypothesized that more virus replication in these animals may have facilitated drug resistance

selection. Reductions in acute viremia are proposed to contribute at a population level to a decrease in virus transmissibility.

Example 10

Single Dosing

The process of Example 7 is repeated in Group 3 with drugs only being administered 2 hours prior to and 22 hours subsequent to each inoculation. The resultant survival curves are comparable to those detailed in Example 8.

Example 11

Single Dosing with Suppository

A group of 6 macaques received the drug treatment of Group 3 per Example 7 in the form of a gel inserted rectally containing 300 mg of tenofovir and 300 mg lamuvidine (3-TC) 1 hour before viral inoculation with observation to assure that the suppository is not voided. The gel is formed by compounding tenofovir and 3-TC in 2% by weight hydroxyethyl cellulose (HEC)-based gel in both a vaginal formulation (pH 4.5) and rectal formulation (pH 6.5) containing (w/v) 3% tenofovir, and 3% 3-TC. The gels are stable at room temperature for at least five months with no loss in activity; and gels retained full activity at both pH 4.5 and pH 6.5 at levels equivalent to those observed for tenofovir and 3-TC preparations in water. Using an MT4/MTT phenotypic assay, all gels were tested for activity against wild-type HIV-1_{HXB2}, and resistant HIV-1 viruses containing the K65R or M184V mutations. No significant cytotoxicity is seen in the cervical explant model.

Viral protection of the macaques is maintained throughout the study.

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Patent documents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These documents and publications are incorporated herein by reference to the same extent as if each individual document or publication was specifically and individually incorporated herein by reference.

The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the invention.

The invention claimed is:

1. 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, wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate, wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally,

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

2. The process of claim 1, wherein selecting a primate host comprises selecting an adult human not infected with the immunodeficiency retrovirus.

3. The process of claim 2, wherein the adult primate host is a male adult primate host.

4. The process of claim 1, wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir disoproxil fumarate, are administered directly to a human in a combined single dosage formulation.

5. The process of claim 1, wherein the immunodeficiency retrovirus is a human immunodeficiency virus.

6. The process of claim 5, wherein a human immunodeficiency virus (HIV) is HIV-1.

7. The process of claim 1, wherein the combination is administered as preexposure prophylactic treatment prior to rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus.

8. The process of claim 1, comprising administering 200 milligrams (mg) of emtricitabine and 300 mg of tenofovir disoproxil fumarate to a human host.

9. The process of claim 1, wherein the combination is administered daily for several days, weeks or months.

10. The process of claim 9, wherein 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.

11. The process of claim 1, wherein administration of the combination results in an absence of persistent viremia and seroconversion of the primate host.

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine wherein the pharmaceutically effective amount of the emtricitabine is administered orally, subcutaneously or vaginally; and

ii. a pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate wherein the pharmaceutically effective amount of the tenofovir or tenofovir disoproxil fumarate is administered orally, subcutaneously or vaginally;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human.

13. The process of claim 12, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

14. The process of claim 12, wherein the combination is compounded into a single combination formulation.

15. The process of claim 12, wherein an inhibition of infection in the host is determined by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.

16. The process of claim 12, wherein the combination is administered following potential exposure of the primate host to the human immunodeficiency retrovirus.

17. The process of claim 16, wherein the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.

* * * * *

US009937191B2

(12) **United States Patent**
Heneine et al.

(10) **Patent No.: US 9,937,191 B2**
(45) **Date of Patent: *Apr. 10, 2018**

(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(Continued)

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CPC ***A61K 31/675*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 31/513*** (2013.01)

(58) **Field of Classification Search**
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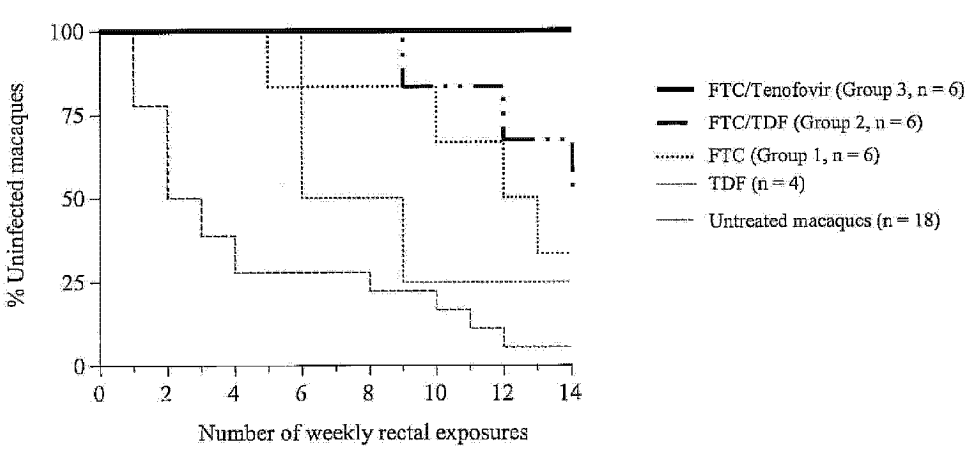
(57) **ABSTRACT**

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose within 24 hours of the exposure. A regime of regular daily doses is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for
(Continued)



controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection the detailed combination prior to sexual exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

19 Claims, 4 Drawing Sheets

Related U.S. Application Data

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USPC 514/81, 274
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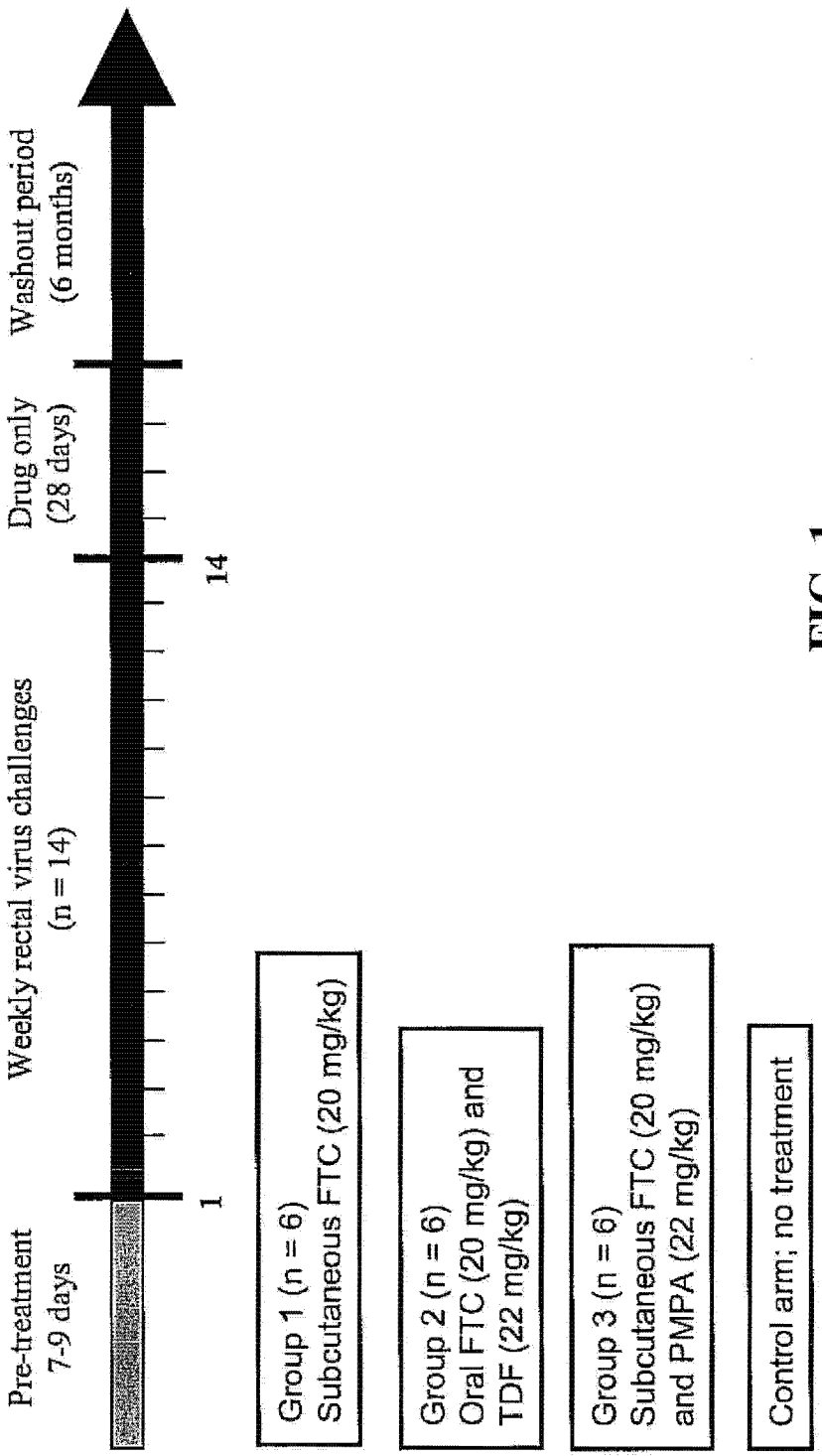
Pre-treatment
7-9 days
Weekly rectal virus challenges
(n = 14)
Drug only
(28 days)
Washout period
(6 months)
1
14
Group 1 (n = 6)
Subcutaneous FTC (20 mg/kg)
Group 2 (n = 6)
Oral FTC (20 mg/kg) and
TDF (22 mg/kg)
Group 3 (n = 6)
Subcutaneous FTC (20 mg/kg)
and PMPA (22 mg/kg)
Control arm; no treatment

FIG. 1

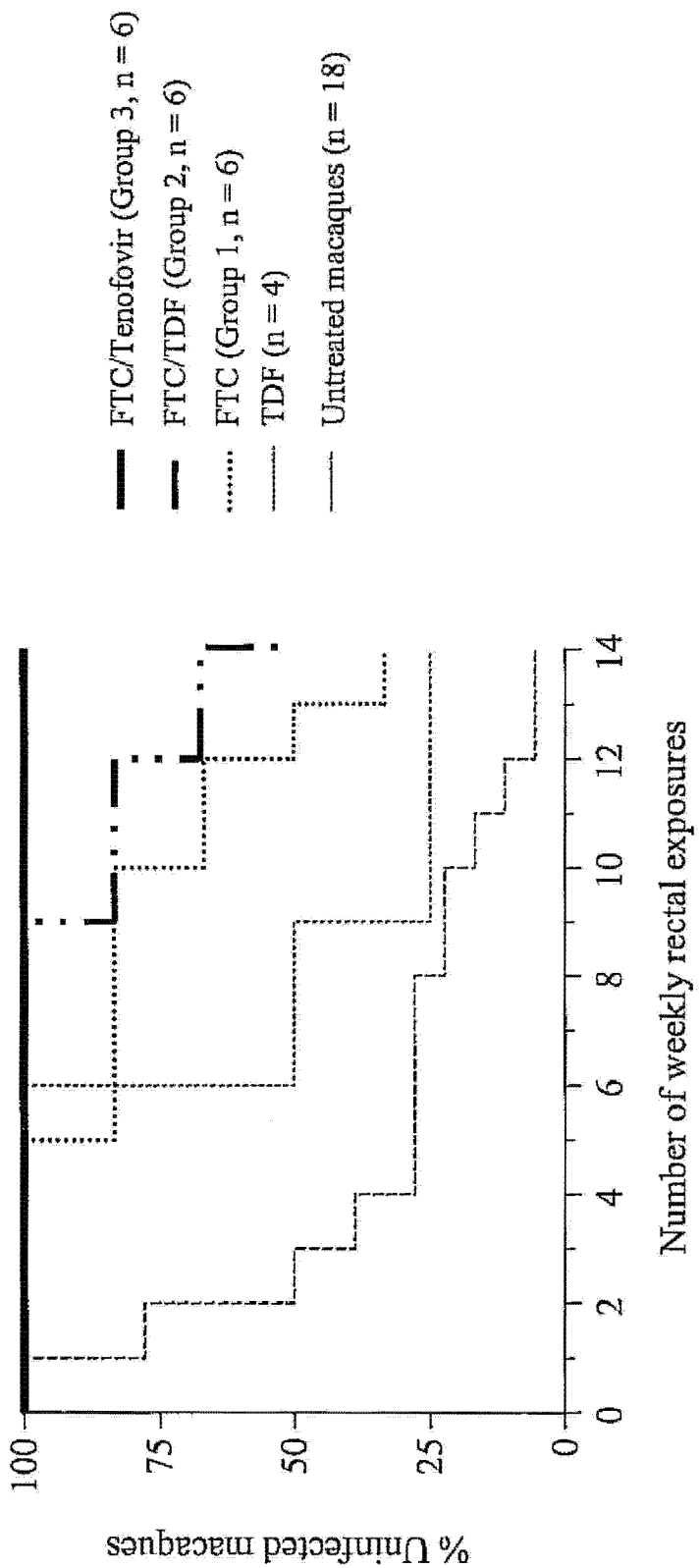
FTC/Tenofovir (Group 3, n = 6)
FTC/TDF (Group 2, n = 6)
FTC (Group 1, n = 6)
TDF (n = 4)
Untreated macaques (n = 18)
% Uninfected macaques
100
75
50
25
0
0
2
4
6
8
10
12
14
Number of weekly rectal exposures

FIG. 2

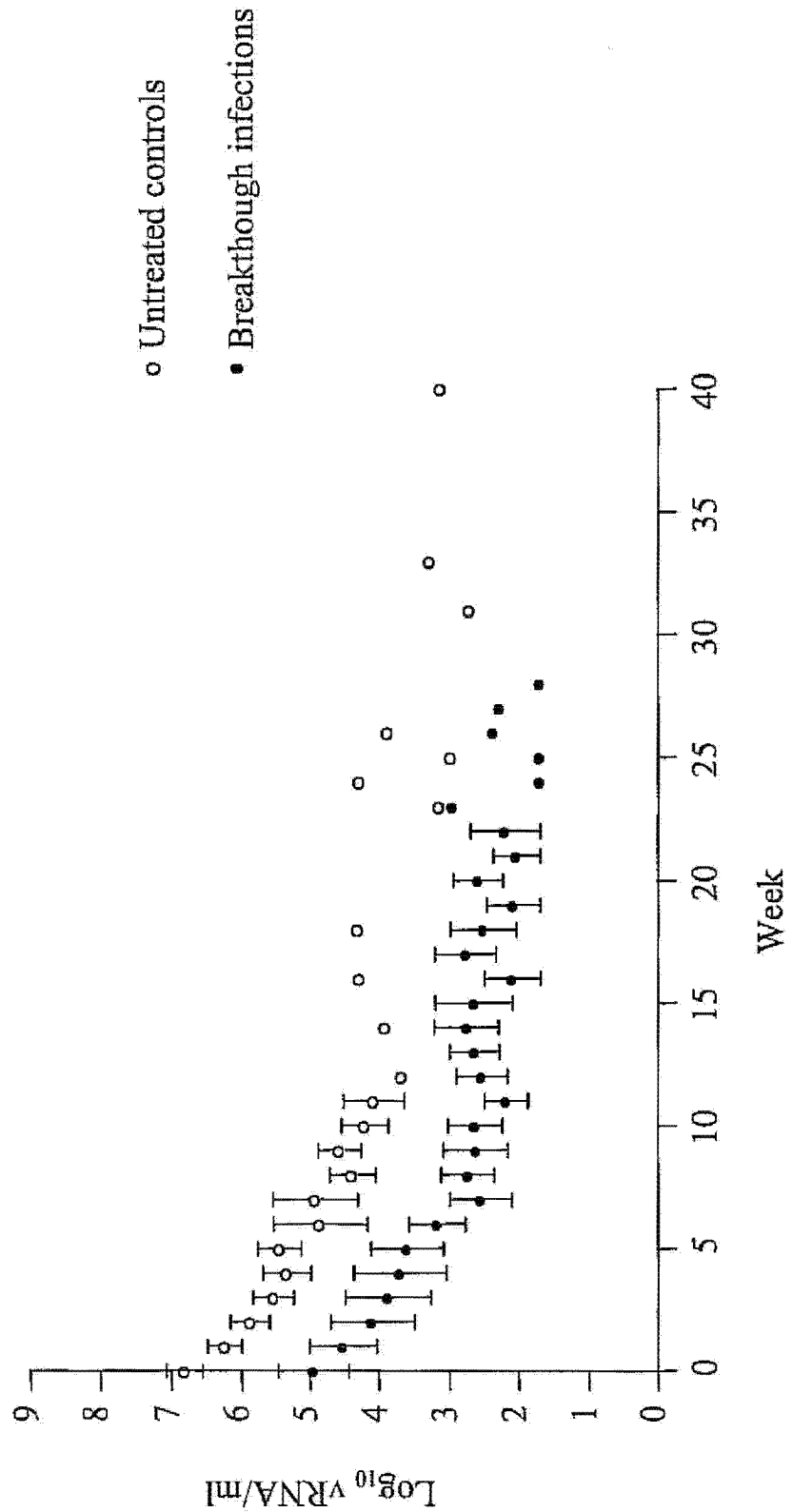
o Untreated controls
• Breakthough infections
Log10 vRNA/ml
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30
35
40
Week

FIG. 3

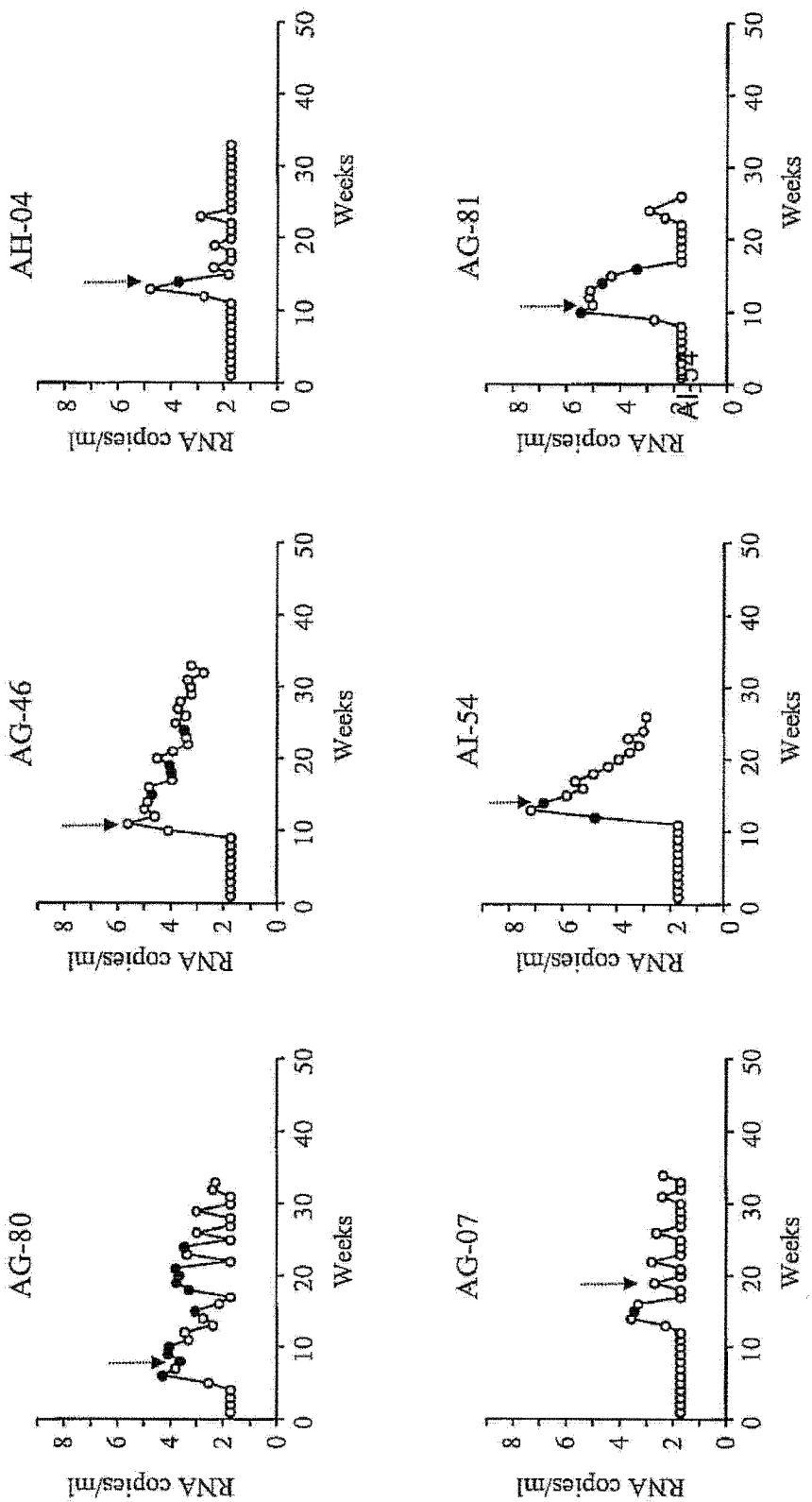
AH-04
AG-81
AG-46
AI-54
AG-80
AG-07
RNA copies/ml
Weeks
0
2
4
6
8
10
20
30
40
50

FIG. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation U.S. patent application Ser. No. 14/679,887, filed on Apr. 6, 2015, which is a continuation of U.S. patent application Ser. No. 11/669,547, filed on Jan. 31, 2007, issued as U.S. Pat. No. 9,044,509, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on Feb. 3, 2006. All of the prior applications are incorporated herein by reference in their entirety.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

The present invention in general relates to a process for inhibiting initial infection by a retrovirus such as human immunodeficiency virus (HIV) and in particular to a combination of a nucleoside reverse transcriptase inhibitor (NRTI) and a nucleotide reverse transcriptase inhibitor (NtRTI) capable of preventing self-replicating retroviral infection, even in response to multiple viral challenges.

BACKGROUND OF THE INVENTION

Despite the fact that significant progress has been made slowing the advancement of the symptoms of AIDS associated with HIV infection, in the absence of an effective vaccine, HIV continues to spread globally. The spread of HIV persists in part because an infected individual remains a potential source of injection. It is clear that current treatment of monitoring viral titer and in response to a titer exceeding a preselected threshold commencing treatment with highly active antiretroviral therapy (HAART) has not prevented new infections.

An attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment. As HIV and, in particular HIV-1, often begins with a comparatively small population of retroviral particles being transmitted to a new host and within a few days self-replicating into a retroviral titer detectable in host blood serum. 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.

Previous attempts at pre-exposure prophylaxis have met with limited success. Prophylactic activity has been demonstrated with the NtRTI, tenofovir in monkey models challenged with simian immunodeficiency virus (SIV).[1-3] Unfortunately, oral daily dosing and pre-exposure prophylaxis with tenofovir at a dose equivalent to that used in humans proved to only be partially protective against rectal SHIV transmission.[4]

HAART therapy involves the administration of a combination including at least three active compounds classified by the mode of operation as an NRTI, an NtRTIs, a non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitor, and an entry inhibitor. While HAART is effective in lowering retroviral titer in a host, concerns remain as to the long term toxicity and the retained potential to infect others. It is also unknown if initiating HAART therapy in a pre-exposure prophylactic regimen would be efficacious. As a result, society remains devoid of a pre-exposure prophylactic regimen to prevent an individual from developing self-propagating retrovirus infection subsequent to initial exposure.

Thus, there exists a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population. There also exists a need for a chemoprophylactic composition formulated with a vehicle amenable to user compliance.

SUMMARY OF THE INVENTION

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose prior to the exposure. A regime of multiple temporally spaced doses prior to retroviral exposure is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection a combination of a pharmaceutically effective nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

A kit is also provided that includes at least one combination dose of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor sufficient to protect a primate host from developing a self-replicating retroviral infection along with instructions for the administration of the at least one dose one prior to and optionally one additional dose subsequent to a potential exposure to an immunodeficiency retrovirus along with dosing modifications associated with subject characteristics and behaviors to further reduce the risk of contracting a self-replicating immunodeficiency retrovirus infection.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic depicting one study of the present invention for 4 groups of macaques in which all treated macaques received known antiretroviral medications 7 to 9 days prior to the first virus inoculation and continuing throughout the study with treated animals that remained uninfected throughout the 14 viral challenges receiving 28 additional days of post-exposure prophylactics.

FIG. **2** is a survival curve graph for macaque Groups 1-4 per FIG. **1**, as well as for animals receiving only tenofovir disoproxil fumarate (TDF).

FIG. **3** is a graph depicting a plot of viremia as a function of time for untreated controls (○) and breakthrough infections (●) where each point represents a mean viremia observed, 0 time indicates peak plasma virus load observed in a given animal where the arrow bars denote standard error of the mean (SEM).

FIG. 4 depicts plots of infection dynamics as a function of time during the study per FIG. 1 with plots for animals coded as AG-80, AG-46, AH-04 and AG-07 corresponding to emtricitabine (FTC) treatment alone, or FTC plus TDF treatment (AI-54 and AG-81). The arrow indicates the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in as black full circles. Open circles indicate the time points where no genotype was undertaken

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention has utility in protecting a primate host from self-propagating immunodeficiency virus infection. The use of a combination of antiretroviral agents as a prophylactic dosing regime is also provided for the manufacture of a medicament is provided for protection against a human immunodeficiency virus infection developing to a level of self-replicating infection. Retroviral transmission through most routes entails a new primate host receiving a small number of viral particles. Common routes of retrovirus transmission illustratively include sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, blood transfusions, birth canal exposure, breastfeeding, and transplacental contact between individuals. Through the administration of at least one nucleoside reverse transcriptase inhibitor (NRTI) and at least one nucleotide reverse transcriptase inhibitor (NtRTI) prior to a retrovirus exposure protection is provided against development of a self-replicating retroviral infection. As the aforementioned exposure routes are characterized by a small number of retrovirus particles being transferred to the new primate host, this initial phase of infection represents a window of opportunity to protect a host from infection. The inventive chemoprophylactic treatment is provided through a dosing regimen. A dosing regimen according to the present invention that provides retroviral protection to a host primate includes at least one single dose administered prior to initial retroviral exposure. An inventive dosing regimen also includes a course of multiple doses administered in advance of exposure to maintain a therapeutic level of NRTI and NtRTI agents in the primate host. The timing of the at least one does prior to retroviral exposure is dictated by the pharmacokinetics of the NRTI and NtRTI components to assure the presence of a therapeutically effective amount of inventive composition for at least 20 hours subsequent to the exposure to the communicated small retroviral particle population. Multiple doses are administered according to the present invention at regular time intervals and amounts such as for example like formulated daily doses for a period of several days, weeks, or months; or are administered in advance of a likely exposure as a cluster of doses, with the amount of NRTI and NtRTI components in each dose being independent of the of amount of NRTI and NtRTI in other doses within the cluster. While most oral, topical, and parenteral existing versions of NRTIs and NtRTIs are fully absorbed and therapeutically active within 1 to 8 hours, it is appreciated that subcutaneous implants and long acting timed release formulations allow for a single dose to sustain therapeutically effective amounts of an inventive prophylactic composition for several days, weeks, or even months. Representative of sustained release compositions and implants are provided in the U.S. Pat. Nos. 4,122,129; 4,927,687; 4,996,047; 5,169,642; and 5,656,296.

The combination of NRTI and NtRTI compounds administered prophylactically according to the present invention are shown to provide a dose-dependent inhibition of HIV self-replicating infection and a therapeutically effective dosing primate host protection against self-replicating HIV infection is provided, even in response to multiple viral challenges. While the present invention is largely detailed with respect to HIV-1 as a prototypical infectious and pathogenic retrovirus, it is appreciated that other retroviruses owing to reliance on reverse transcription for replication are also protected against in a primate host according to the present invention.

As used herein, "protection" as used in the context of a host primate response to an immunodeficiency virus challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.

As used herein, the term "retrovirus" is inclusive of any virus that utilizes reverse transcriptase in the viral replication cycle and therefore is susceptible to the antiviral activity of nucleoside or nucleotide analogs specifically inclusive of HIV (HIV-1 and HIV-2), HTLV-1, HTLV-2, HTLV-3, HTLV-4, and SIV. Also encompassed are viruses such as HBV that although not technically classified as retroviruses nonetheless utilize a reverse transcriptase and are therefore susceptible to the antiviral activity of nucleoside and/or nucleotide analogs.

As used herein a "primate host" is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Non-human primates are appreciated to themselves be susceptible to infection by retroviruses and in particular immunodeficiency viruses and represent well-established animal models as to human response with an appreciation that physiological differences often require different doses in milligrams per kilogram for a nonhuman primate animal model relative to a human.

The compositions of the present invention include administration in combination of an NRTI and NtRTI and are readily compounded by pharmaceutical composition with conventional pharmaceutically acceptable carriers or diluents. Additionally, pharmaceutically acceptable derivatives and prodrugs of active NRTIs and NtRTIs operative in the present invention include salts such as alkali metal salts; esters such as acetate, butyrate, octinoate, palmitate, chlorobenzoates, benzoates, C_1-C_6 benzoates, succinates, and mesylate; salts of such esters; and nitrile oxides. It is appreciated that other analogs of pharmaceutically active NRTIs or NtRTIs that provide within a primate host an active antiviral metabolite residue are also suitable as part of an inventive composition. A pharmaceutically acceptable carrier or diluent includes agents that are compatible with other ingredients of a dosage and not injurious to a primate host. The identity and process for compounding a combination of at least one NRTI and at least one NtRTI into a dosage form suitable for delivery by a route with administration by oral, rectal, topical, vaginal or parenteral routes of administration are provided in Remington's Science and Practice of Pharmacology, 20th Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

As used herein the term "prodrug" is defined to include a compound that when administered to a primate host generates an active NRTI or NtRTI as a result of spontaneous reaction under physiological conditions, enzymatic catalysis, metabolic clearance, or combinations thereof. An exemplary NtRTI prodrug currently FDA approved for HAART use is tenofovir disoproxil fumarate (TDF) and is detailed in U.S. Pat. No. 5,935,946.

The present invention provides an alternative to conventional retroviral therapy using HAART, in response to self-propagating HIV infection by protecting a primate host against the establishment of self-replicating retroviral infection that provides an indication for such therapy. Through prophylactic prior dosing with an inventive combination including at least one NRTI and one NtRTI, replication of the comparatively low number of viral particles received by a host primate is prevented.

To achieve protection against a primate host developing a retroviral self-replicating infection, at least one dosage of an NRTI and NtRTI is administered to the primate host prior to exposure to the retrovirus. Preferably, the at least one NRTI and at least one NtRTI are administered concurrently. More preferably, the combination of reverse transcriptase inhibitors is compounded into a single formulation.

The process of the present invention demonstrates protection against retroviral self-replicating infection through administration of even a single dosage administered prior to the retroviral exposure. Owing to the known pK rates of specific NRTIs and NtRTIs, a single dosage is administered to assure a therapeutically effective amount of NRTI and NtRTI persist in the primate host for a time of more than 12 hours after viral challenge. With conventional NRTI and NtRTI formulations, currently approved for HAART, preferably an inventive dose is administered within 12 hours prior to retroviral exposure and still more preferably often within 2 hours prior to retroviral exposure. The practice of the inventive process involving the administration of a single dosage in the hours proceeding a likely retroviral exposure is particularly advantageous in assuring compliant dosing in a human and also avoids side effects associated with a regular dosing regime and is particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure. Preferably, an additional dose or doses of a combination of at least one NRTI and at least one NtRTIs is provided subsequent to the retroviral exposure event to assure adequate antiviral reverse transcriptase inhibitor concentration during and immediately subsequent to retroviral infection of the host founder cell population so as to preclude retroviral self-replication to assure NRTI and NtRTI incorporation into a replicating virus genome. Preferably, a dose of an inventive composition taken after retroviral exposure is administered within 24 hours subsequent to the exposure, and more preferably within 12 hours subsequent to the exposure.

Alternatively, an individual routinely subjected to retroviral exposure can be protected against the development of a self-replicating retroviral infection through administration of regular prophylactic doses of an inventive combination. As a result, an epidemiological advantage exists in controlling the outbreak and spread of a retrovirus within a population is provided through offering routine doses of an inventive composition prophylactically to high-risk persons such as sex workers and a short course prophylactic inventive composition to uninfected sex trade clientele.

It is appreciated that hybrid dosing regimes of an inventive composition are also operative herein and include multiple doses prior to retroviral exposure with multiple doses not being administered for a duration or with sufficient periodicity to arise to the level of a routine prophylactic regime.

The at least one nucleoside reverse transcriptase inhibitor has the attribute of interfering with in vivo viral replication. An NRTI operative in an inventive prophylactic process includes emtricitabine, lamivudine, zalcitabine, zidovudine, azidothymidine, didanosine, stavudine, abacavir; with the aforementioned specific NRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

An at least one nucleotide reverse transcriptase inhibitor (NRTI) present in an inventive composition to protect a primate from developing a self-replicating retroviral infection illustratively includes tenofovir, adefovir; 2',3'-dideoxy-3'-fluoroadenisine; 2',3'-dideoxy-3'-fluoroguanasine; 3'deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine with the aforementioned specific NtRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, and combinations thereof. Representative non-nucleoside reverse transcriptase inhibitors operative herein illustratively include delavirdine, efavirenz, nevirapine, and other diarylpyrimidine (DAPY) derivatives. Representative protease inhibitors operative herein illustratively include amprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, fosamprenavir calcium, ritonavir, atazanavir sulfate nelfinavir mesylate, and combinations thereof. An entry inhibitor operative herein as an optional active ingredient in an inventive composition illustratively includes enfuvirtide, Schering C (Schering Plough), S-1360 (Shionogi), and BMS806 (Bristol Myers Squibb).

The dose of individual active components of an inventive prophylactic composition is administered to create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure. It is appreciated that establishing a therapeutic concentration at the time of viral replication for a given NRTI, NtRTI or optional additional active agent in the target cells, includes factors for the therapeutic agent such as the route of administration, pharmacokinetics, absorption rate based on administration route, effects of food on oral absorption, in vivo distribution, metabolic pathways, elimination route, race, gender, and age of the subject, single dose incident side effects, long term administration side effects, and synergistic effects with co-administered active agents. Information related to these factors considered in dosing are available from the United States Food and Drug Administration (http://www.fda.gov/oashi/aids/virals.html) Preferably, NRTI and NtRTI prophylactic 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.

An inventive kit is provided that includes a 2-dose package of oral doses, such as tablets. In an exemplary embodiment of FDA approved NRTI and NtRTIs, each dose contains between 100 and 2500 milligrams (mg) of emtricitabine and between 100 and 2500 mg of TDF along with instructions to ingest the first dose approximately 1 to 8 hours prior to potential retroviral exposure and preferably about 2 hours there before, and a second dosage to be ingested 20 to 48 hours after potential retroviral exposure, preferably at about 22 hours thereafter. For an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF. A non-human primate dose according to the present invention is typically higher on a mg per kg animal body weight basis by a factor typically ranging from 2 to 10. Additional NRTIs, NtRTIs, NNRTIs, protease inhibitors or entry inhibitors are optionally provided in concert with either or both of these doses. The kit also includes instructions as to the timing of doses, contraindi-

cations, modifications associated with food ingestion, and additional behaviors that the recipient (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. It is also appreciated that a carrier illustratively including a gel, jelly, cream, ointment, film, sponge, foam, suppository, vaginal ring or other delivery device is provided containing an NRTI such as emtricitabine, alone or in combination with an NtRTI such as tenofovir or TDF. The carrier is readily applied to mucosal tissue likely to be exposed to viral transmission as an added level of protection in concert with the oral doses.

An inventive kit is also provided that includes at least one NRTI and at least one NtRTI compounded as a gel, jelly, cream, ointment, film, sponge, foam, suppository, or applied to a vaginal ring or other like antiviral barrier. To prepare such a pharmaceutical compounded form, an effective amount of each of the active agents inclusive of at least one NRTI and NtRTI is combined in admixture with the pharmaceutically acceptable carrier or applied to a surface of the barrier. It is appreciated that the residence time of such a pharmaceutical composition is maintained at the site of administration through the inclusion of an optional bioadhesive that provides adhesion to mucosal tissue or the dermis. An inventive composition compounded for application to the dermis or mucosal tissue is provided along with instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the person (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. Optionally, a kit containing an oral dosage is combined with a composition compounded for application to the dermis, rectal mucosa or vaginal mucosa so as to assure a therapeutically effective combination of NRTI and NtRTI at the mucosal point of retroviral entry associated with sexual exposure, as well as a therapeutically effective serum circulating quantity of prophylactic antiretrovirals.

The present invention is further detailed with respect to the following non-limiting examples. These examples are intended to provide exemplary specific embodiments of the present invention and are not intended to limit the scope of the appended claims.

EXAMPLES

Example 1—Antiretroviral Drugs and Doses

A dose of 22 mg/kg of tenofovir disoproxil fumarate (TDF) is given orally and 20 mg/kg of emtricitabine (FTC) given orally or subcutaneously to one group of adult male rhesus macaques. The 22 mg/kg TDF dose resulted in an area-under the plasma concentration-time curve over a 24 h interval (AUC) of 4.49 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×hr/ml)[6]. Subcutaneous administration of FTC results in plasma FTC levels comparable to those achieved during oral administration, indicating a high FTC absorption in rhesus macaques.

Oral administration of FTC and TDF to macaques is by mixing the drug powders with peanut butter or fruit. Macaques are observed to ensure ingestion.

Example 2—Virus Inoculations

A chimeric envelope $SHIV_{SF162P3}$ isolate is used to inoculate the macaques. $SHIV_{SF162P3}$ is a construct that contains the tat, rev, and env coding regions of $HIV\text{-}1_{sF162}$ in a background of SIVmac239. This isolate was obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.[7,8] Virus exposures are performed 2 hours after drug treatment, and involved non-traumatic inoculation of 1 mL of $SHIV_{SF162P3}$ (10 TCID50 or 7.5×10^6 viral RNA copies) into the rectal vault via a sterile gastric feeding tube.[9] Anesthetized macaques remained recumbent for at least 15 min after each intrarectal inoculation.

Example 3—SHIV Viral Load Assay

Plasma RNA is quantified using a real-time PCR assay as previously described.[5] This assay has a sensitivity of detection of 50 RNA copies/ml or 10 copies of a pVp1 plasmid carrying the SIVmac239 RT gene. HIV-1 RNA is extracted from 1 mL of plasma using the NucliSens extraction method (bioMérieux). A known amount of virus particles (3×10^5) from an HIV-1 CM240 virus stock is added to each sample prior to extraction to control for the efficiency of extraction. Reverse transcription is performed using 10 microliters (μl) of extracted RNA and the 2-step TaqMan Gold reverse-transcriptase (RT)-PCR kit (Applied Biosystems) according to the manufacturer's instructions. PCR reactions are performed as described using an ABI 7000 Gene Detection System (Applied Biosystems). Virus loads are calculated from a standard curve generated with known amount of virus particles. All primers and probes used for SIVmac239 and HIV-1 CM240 have been reported elsewhere.[5] HIV-1 CM240 is obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.

Example 4—Detection of Genotypic Resistance to FTC and Tenofovir

Emergence of FTC and tenofovir resistance is monitored by sequence analysis of SIV RT (551 bp; amino acids 52 to 234) and by a more sensitive allele-specific real-time PCR method for the K65R and M184V mutations. Sequence analysis was done from plasma viruses using an RT-PCR procedure as previously described.[5] The Vector NTI program (Version 7, 2001) is used to analyze the data and to determine deduced amino-acid sequences. Detection of low frequency of K65R and M184V mutants in plasma by real-time PCR is performed as previously described.[10] These assays have a detection limit of 0.4% of K65R and 0.6% of M184V cloned sequences in a background of wild type plasmid.

Example 5—Virus-Specific Antibody Responses

Virus-specific serologic responses (IgG and IgM) are measured using a synthetic-peptide EIA (Genetic Systems HIV-1/HIV-2) assay.

Example 6—Statistical Methods

The exact log-rank test is used for a discrete-time survival analysis of the treatment and control groups, with use of the number of inoculations as the time variable. The Cox proportional hazards model is used to estimate the relative hazard ratio (HR). Percent protection is calculated from the HR value using the formula: (1-1/HR)×100. All statistical analyses for calculation of the efficacy of the different

interventions are performed using SAS software (version 9.1; SAS Institute) and StatXact software (version 6.3; Cytel).

Example 7—Routine Dosing Experimental Design

Macaques are exposed rectally once weekly for up to 14 weeks to SHIV162p3 which contains an R5 tropic HIV-1 envelope that resembles naturally transmitted viruses. The SHIV162p3 challenge dose is 10 TCID50 or 7.6×10^5 RNA copies which is similar to HIV-1 RNA levels in semen during acute infection in humans.[11] Virus exposures are terminated when a macaque became infected. FIG. **1** shows the study design and the interventions evaluated in each group of macaques. Three prophylactic drug treatments of increasing drug potency are each given once daily to a group of six macaques. Animals in Group 1 were treated subcutaneously with 20 mg/kg of FTC alone. Animals in Group 2 received orally a combination of FTC (20 mg/kg) and TDF (22 mg/kg). Animals in Group 3 had the most protective treatment with subcutaneous 20 mg/kg of FTC and a 22 mg/kg of tenofovir (PMPA). The rate of infection in each group is compared with that seen in 18 untreated control macaques (9 real time and 9 historical controls).

All treated macaques received the corresponding drugs 7 to 9 days prior to the first virus inoculation to achieve steady-state plasma levels. Treated animals that remained uninfected during the 14 challenges received 28 days of post-exposure prophylaxis after the last challenge. Protection was defined as absence of persistent viremia and seroconversion. Treated animals that became infected continued treatment for an average of 21 weeks (range=13 to 29) to monitor for plasma viremia and drug resistance development.

Example 8—Survival Curves

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/kg) is also provided for comparison. Untreated macaques are infected after a median of 2 rectal exposures (mean=4). The majority of the animals (13/18 or 72%) are infected during the first 4 challenges (median=2); 4 (22%) are infected between exposures 8 and 14 (mean=10), and only 1 (6%) remained uninfected after 14 exposures. The median 2 exposures for infection in controls suggests that an animal receiving prophylactic treatment and remaining uninfected after 14 virus challenges would have been protected against a median of 7 rounds of transmissions. Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed. All 6 macaques in Group 3 that received the most potent inventive composition remained uninfected demonstrating that full protection against repeated challenges is possible. Of the 6 macaques in Group 2, 4 were protected and only 2 (animal reference numbers AI-54 and AG-81) became infected at exposures 9 and 12. Compared to controls, infection in this group is reduced by 7.8-fold (Cox proportional hazard ratio [HR]=7.8, p=0.0075). Infection in both animals is significantly delayed compared to the untreated controls (p=0.0004). These 2 macaques became seropositive 2 weeks after the first detectable viral RNA in plasma and both were proviral DNA positive at weeks 10 and 12, respectively. Of the 6 macaques in Group 1 receiving FTC only, 2 remained protected after 14 exposures and 4 had the first detectable viral RNA at exposures 5 (AG-80), 10 (AG-46), 12 (AH-04), and 13 (AG-07), respectively. Survival analysis showed a statistically significant difference from untreated controls (p=0.004). Compared to controls, infection is reduced 3.8-fold macaques (Cox proportional hazard ratio [HR]=3.8, p=0.021). Infection in these 4 animals is also confirmed by PCR amplification of proviral DNA from PBMCs and by serology; antibody responses are detectable 3, 1, 2, and 6 weeks after the first detectable RNA, respectively. FIG. **2** also shows that the protection achieved with FTC alone was higher than that previously seen in 4 animals receiving TDF,[5] consistent with the slightly higher potency of FTC, although the difference was not statistically significant (p=0.5).

Example 9—Prophylactic Breakthrough Infections and Drug Resistance Emergence

Since the dynamics of breakthrough infections that occur during inventive prophylaxis and drug resistance emergence are unknown, the 6 infected animals from Groups 1 and 2 are followed under continued drug treatment. FIG. **3** compares the virus load kinetics in the 6 breakthrough infections with those in 12 untreated macaques that had sufficient follow-up samples. The mean peak viremia in the 6 treated macaques was 4.9 ± 0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9 ± 0.3 $\log_{10}$ RNA). FIG. **3** also shows that such differences in viremia were maintained up to week 11 as indicated by similar rate of virus load decline seen in the two groups of animals (-0.23 ± 0.02 $\log_{10}$/week in treated vs. -0.29 ± 0.02 $\log_{10}$/week in untreated controls). The individual virus load kinetics in the 6 breakthrough infections are shown in FIG. **4**. Three FTC (AG-80, AH-04, and AG-07) and one of the FTC/TDF (AG-81) failures had undetectable virus loads 3, 4, 7, and 11 weeks after the peak in viremia, respectively; viremia in these animals remained consistently low or undetectable for up to 20 weeks. In contrast, all 12 untreated macaques had detectable virus loads during a median follow-up period of 7 weeks (range=5-36 weeks). The arrow in FIG. **4** denotes the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in black full circles. Open circles are provided for data points not genotyped.

Drug resistance testing showed that wild type virus initiated all 6 breakthrough infections in Groups 1 and 2 reflecting residual virus replication in target cells not protected by drugs (FIG. **4**). Four animals had no evidence of drug resistance despite extended treatment (median=23 weeks). Only 2 animals had detectable M184V (AG-46, FTC-treated) or M1841 (AI-54 FTC/TDF-treated) mutations associated with FTC resistance at week 4 and 10, respectively. The tenofovir-associated K65R mutation is not detected in the 2 Group 2 animals receiving FTC/TDF. FIG. **4** also shows that the 2 macaques that selected M184V/I had the highest peak viremias. Without intending to be bound to a particular theory, it is hypothesized that more virus replication in these animals may have facilitated drug resistance selection. Reductions in acute viremia are proposed to contribute at a population level to a decrease in virus transmissibility.

Example 10—Single Dosing

The process of Example 7 is repeated in Group 3 with drugs only being administered 2 hours prior to and 22 hours subsequent to each inoculation. The resultant survival curves are comparable to those detailed in Example 8.

Example 11—Single Dosing with Suppository

A group of 6 macaques received the drug treatment of Group 3 per Example 7 in the form of a gel inserted rectally containing 300 mg of tenofovir and 300 mg lamuvidine (3-TC) 1 hour before viral inoculation with observation to assure that the suppository is not voided. The gel is formed by compounding tenofovir and 3-TC in 2% by weight hydroxyethyl cellulose (HEC)-based gel in both a vaginal formulation (pH 4.5) and rectal formulation (pH 6.5) containing (w/v) 3% tenofovir, and 3% 3-TC. The gels are stable at room temperature for at least five months with no loss in activity; and gels retained full activity at both pH 4.5 and pH 6.5 at levels equivalent to those observed for tenofovir and 3-TC preparations in water. Using an MT4/MTT phenotypic assay, all gels were tested for activity against wild-type HIV-1_{HXB2}, and resistant HIV-1 viruses containing the K65R or M184V mutations. No significant cytotoxicity is seen in the cervical explant model.

Viral protection of the macaques is maintained throughout the study.

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Patent documents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These documents and publications are incorporated herein by reference to the same extent as if each individual document or publication was specifically and individually incorporated herein by reference.

The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the invention.

The invention claimed is:

1. 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 orally in tablet form prior to the exposure of the primate host to the immunodeficiency retrovirus,

thereby protecting the primate host from infection with the immunodeficiency retrovirus.

2. The process of claim **1**, wherein selecting a primate host comprises selecting an adult human not infected with the immunodeficiency retrovirus.

3. The process of claim **2**, wherein the adult human is a male.

4. The process of claim **2**, wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir or the tenofovir disoproxil fumarate, are administered directly to the human in a combined single tablet.

5. The process of claim **2**, wherein the immunodeficiency retrovirus is a human immunodeficiency virus.

6. The process of claim **5**, wherein a humans immunodeficiency virus (HIV) is HIV-1.

7. The process of claim **1**, wherein the combination is administered as preexposure prophylactic treatment prior to rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus.

8. The process of claim **1**, comprising administering 200 milligrams (mg) of emtricitabinc to the primate host.

9. The process of claim 1, wherein the combination is administered daily for several days, weeks or months.

10. The process of claim 9, wherein 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.

11. The process of claim 1, wherein administration of the combination results in an absence of persistent viremia and seroconversion of the primate host.

12. The process of claim 4, wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disproxil fumarate.

13. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine in a tablet; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir disoproxil fumerate in a tablet;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to a potential exposure of the human to the human immunodeficiency retrovirus.

14. The process of claim 13, wherein the combination is compounded into a single tablet.

15. The process of claim 13, wherein an inhibition of infection in the host is determined by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.

16. The process of claim 13, wherein the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.

17. The process of claim 13, wherein:

(i) the pharmaceutically effective amount of emtricitabine; and

(ii) the pharmaceutically effective amount of tenofovir or tenofovir disoproxil fumarate; are formulated in a single tablet.

18. The process of claim 17, wherein the tablet comprises 200 milligrams of emtricitabine and 300 mg of tenofovir disproxil fumarate.

19. The process of claim 17, wherein the tablet is administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus.

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(54) **INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS**

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(Continued)

(58) **Field of Classification Search**
CPC A61K 31/7072; A61K 31/676
(Continued)

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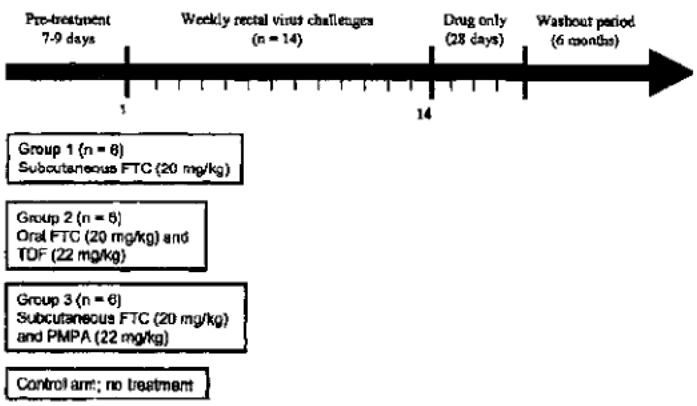
(57) **ABSTRACT**

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose within 24 hours of the exposure. A regime of regular daily doses is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for
(Continued)



Joint Exhibit
JTX 4
1:19-cv-2103-MN

controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection the detailed combination prior to sexual exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

19 Claims, 4 Drawing Sheets

Related U.S. Application Data

continuation of application No. 14/679,887, filed on Apr. 6, 2015, now Pat. No. 9,579,333, which is a continuation of application No. 11/669,547, filed on Jan. 31, 2007, now Pat. No. 9,044,509.

(60) Provisional application No. 60/764,811, filed on Feb. 3, 2006.

(51) **Int. Cl.**

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A61K 31/7072	(2006.01)
A61K 45/06	(2006.01)
A61K 31/683	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/683*** (2013.01); ***A61K 31/7072*** (2013.01); ***A61K 45/06*** (2013.01); *A61K 9/0034* (2013.01)

(58) **Field of Classification Search**
USPC 514/81, 274
See application file for complete search history.

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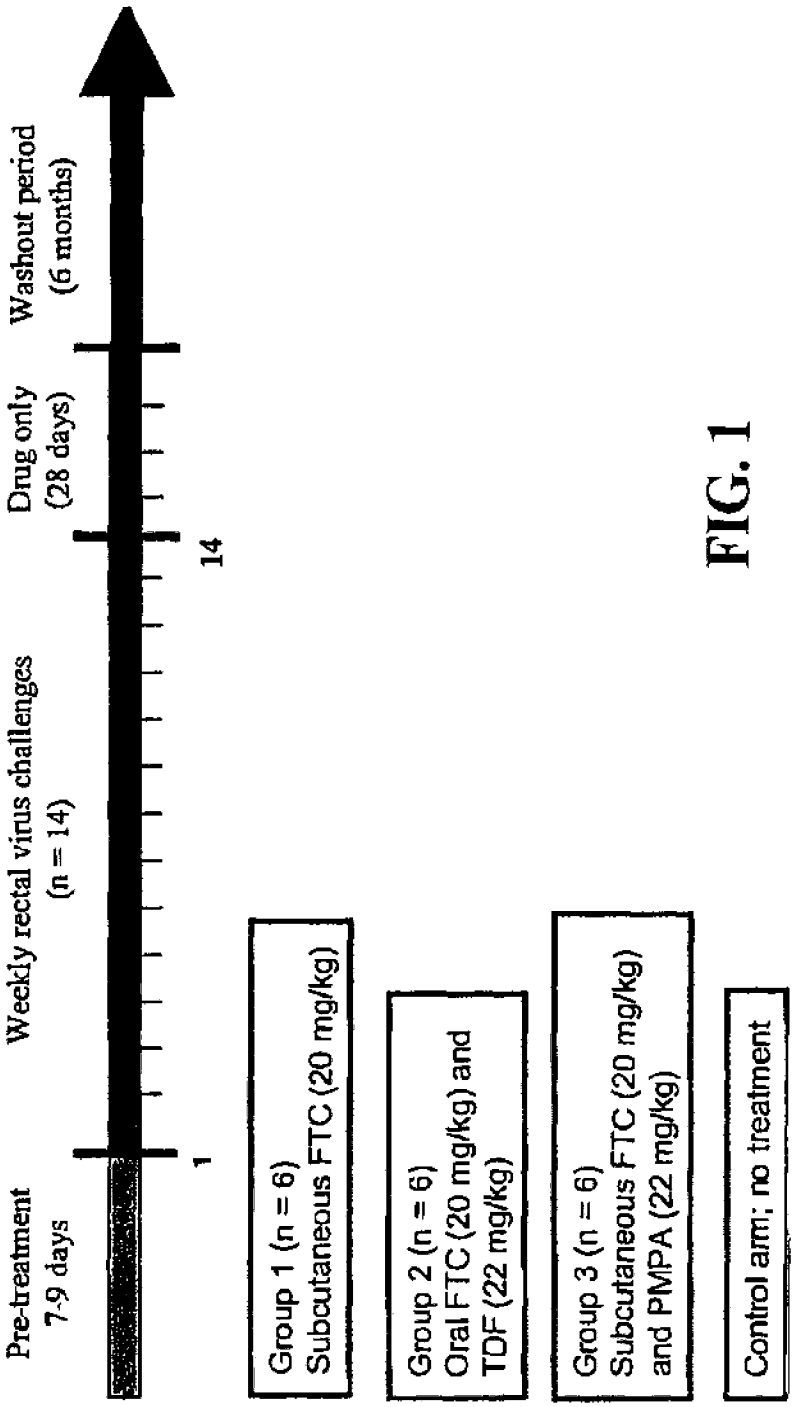
Pre-treatment
7-9 days
Weekly rectal virus challenges
(n = 14)
Drug only
(28 days)
Washout period
(6 months)
1
14
Group 1 (n = 6)
Subcutaneous FTC (20 mg/kg)
Group 2 (n = 6)
Oral FTC (20 mg/kg) and
TDF (22 mg/kg)
Group 3 (n = 6)
Subcutaneous FTC (20 mg/kg)
and PMPA (22 mg/kg)
Control arm; no treatment

FIG. 1

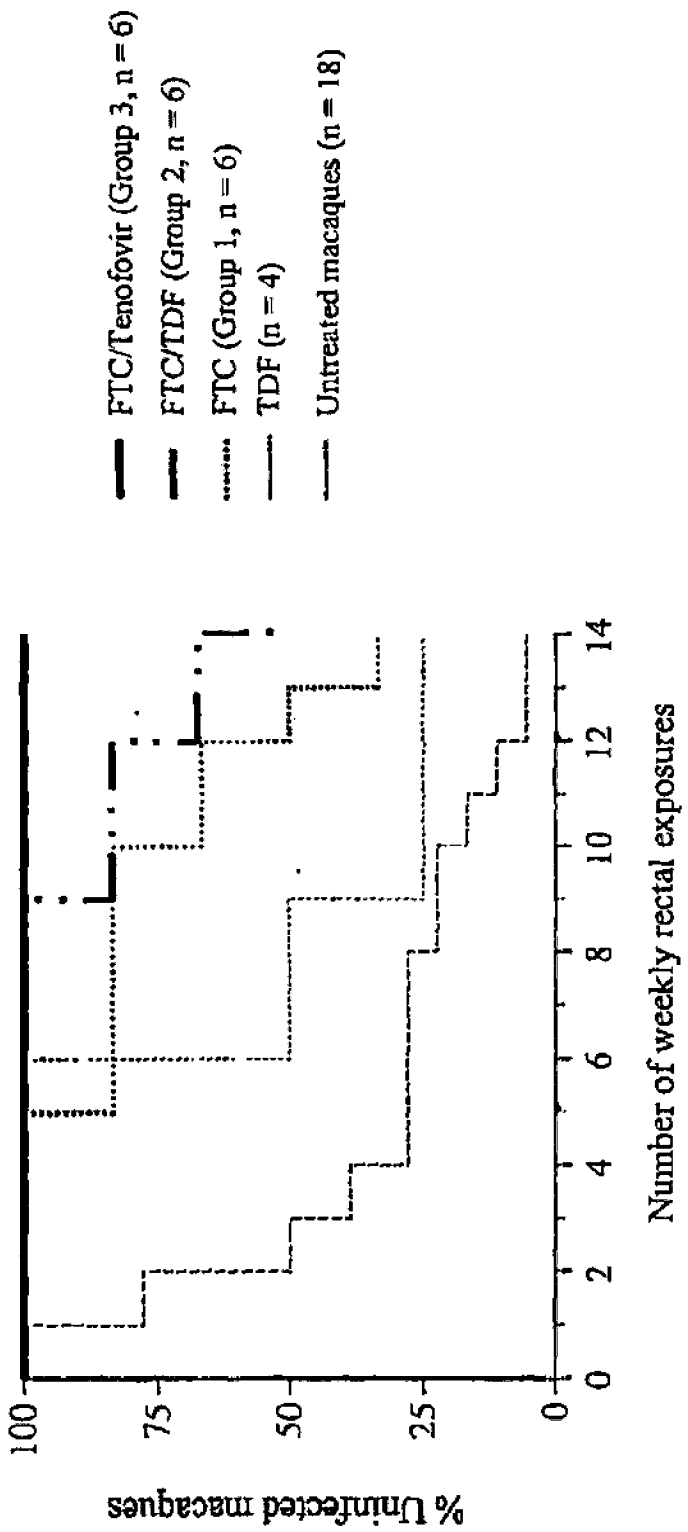
FTC/Tenofovir (Group 3, n = 6)
FTC/TDF (Group 2, n = 6)
FTC (Group 1, n = 6)
TDF (n = 4)
Untreated macaques (n = 18)
% Uninfected macaques
100
75
50
25
0
0
2
4
6
8
10
12
14
Number of weekly rectal exposures

FIG. 2

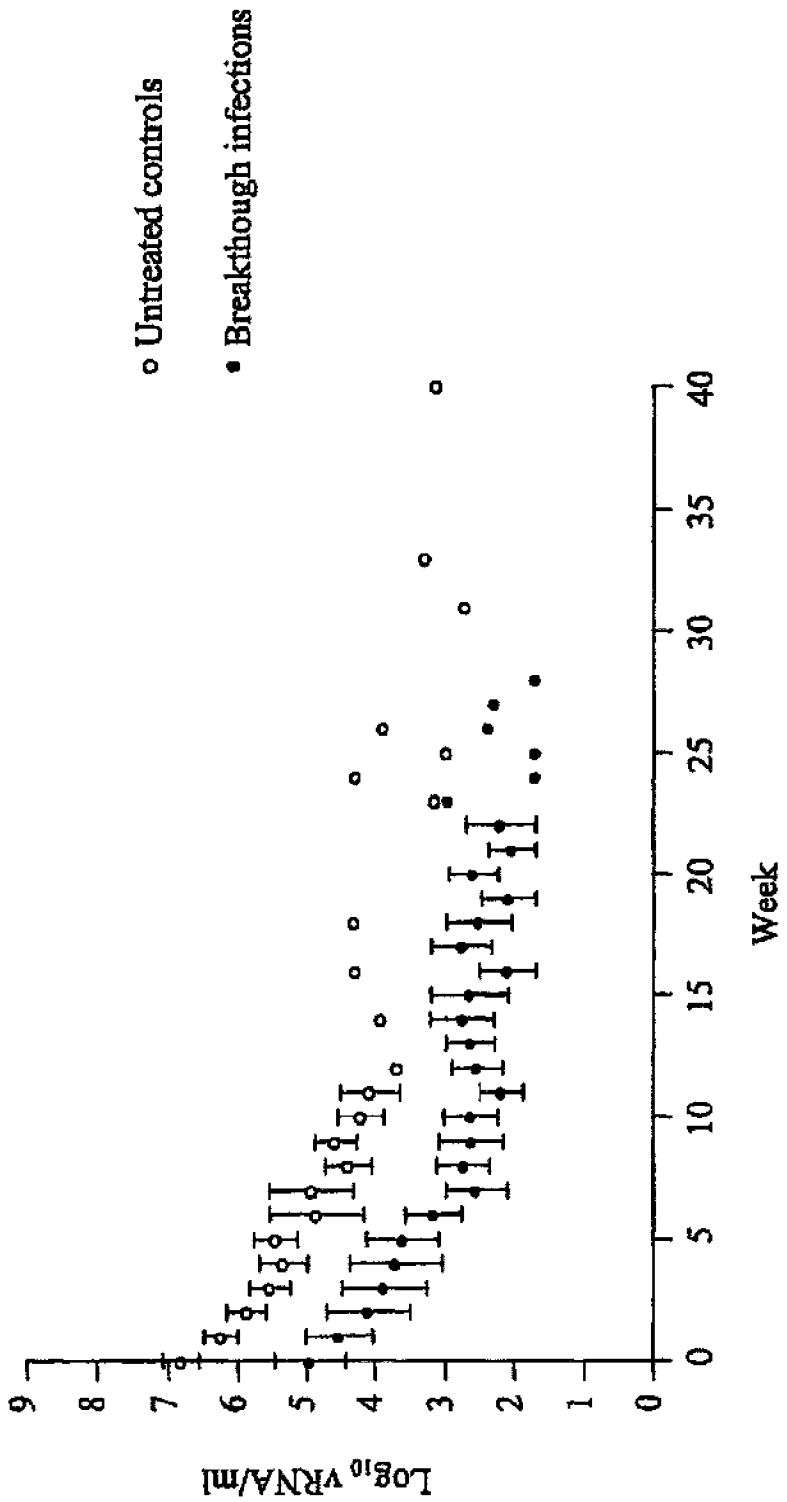
o Untreated controls
• Breakthough infections
Log10 vRNA/ml
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30
35
40
Week

FIG. 3

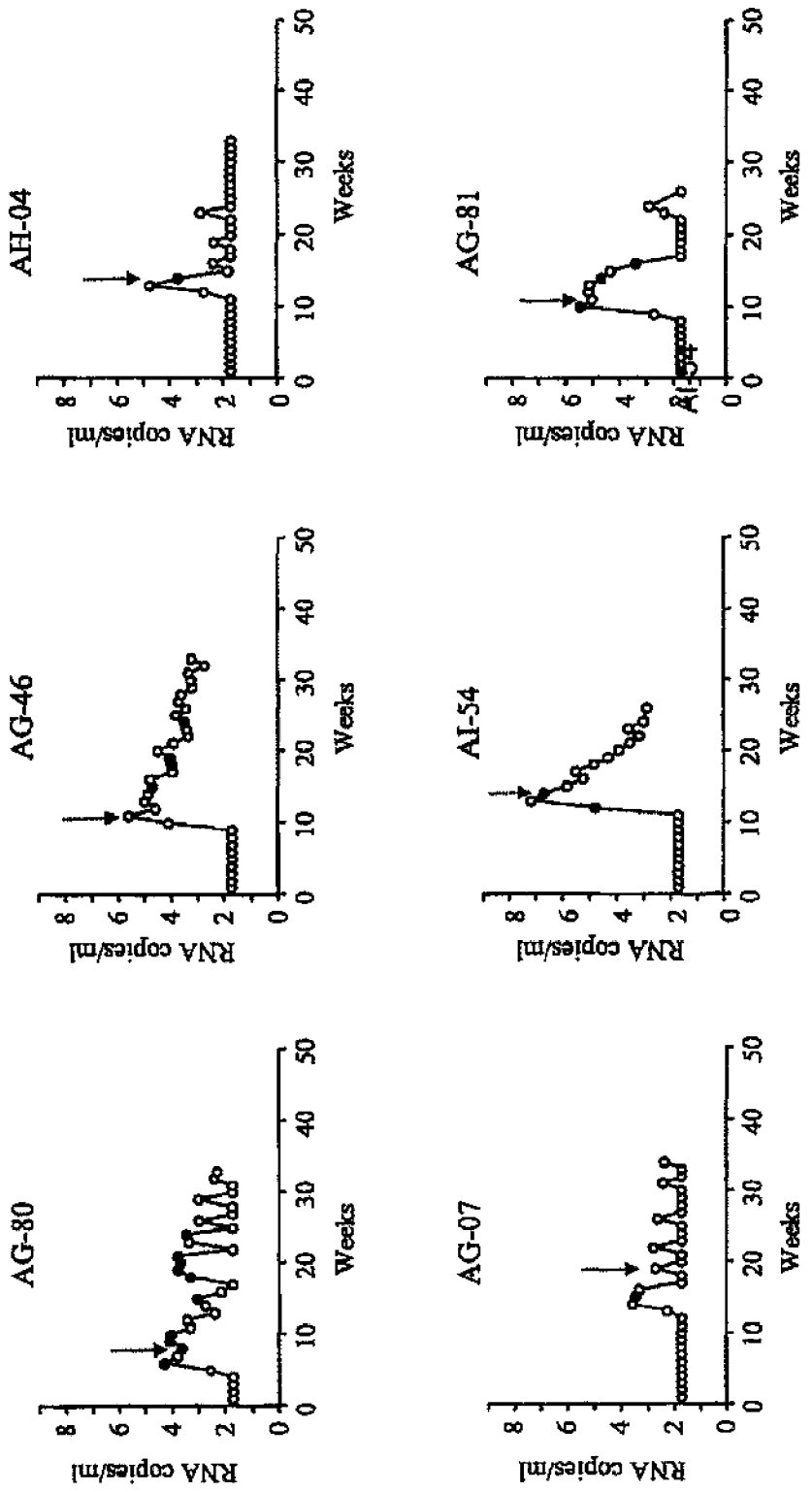
AH-04
AG-81
AG-46
AI-54
AG-80
AG-07
RNA copies/ml
Weeks
0
2
4
6
8
0
10
20
30
40
50

FIG. 4

INHIBITION OF HIV INFECTION THROUGH CHEMOPROPHYLAXIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. patent application Ser. No. 15/406,344, filed on Jan. 13, 2017, which is a continuation U.S. patent application Ser. No. 14/679,887, filed on Apr. 6, 2015, issued as U.S. Pat. No. 9,579,333, which is a continuation of U.S. patent application Ser. No. 11/669,547, filed on Jan. 31, 2007, issued as U.S. Pat. No. 9,044,509, which in turn claims the benefit of U.S. provisional application 60/764,811, filed on Feb. 3, 2006. All of the prior applications are incorporated herein by reference in their entirety.

GOVERNMENT INTEREST

The invention described herein may be manufactured, used, and licensed by or for the United States Government.

FIELD OF THE INVENTION

The present invention in general relates to a process for inhibiting initial infection by a retrovirus such as human immunodeficiency virus (HIV) and in particular to a combination of a nucleoside reverse transcriptase inhibitor (NRTI) and a nucleotide reverse transcriptase inhibitor (NtRTI) capable of preventing self-replicating retroviral infection, even in response to multiple viral challenges.

BACKGROUND OF THE INVENTION

Despite the fact that significant progress has been made slowing the advancement of the symptoms of AIDS associated with HIV infection, in the absence of an effective vaccine, HIV continues to spread globally. The spread of HIV persists in part because an infected individual remains a potential source of injection. It is clear that current treatment of monitoring viral titer and in response to a titer exceeding a preselected threshold commencing treatment with highly active antiretroviral therapy (HAART) has not prevented new infections.

An attractive method of controlling the spread of HIV would be to provide an individual exposed to a potential source of HIV with a pre-exposure prophylactic treatment. As HIV and, in particular HIV-1, often begins with a comparatively small population of retroviral particles being transmitted to a new host and within a few days self-replicating into a retroviral titer detectable in host blood serum. 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.

Previous attempts at pre-exposure prophylaxis have met with limited success. Prophylactic activity has been demonstrated with the NtRTI, tenofovir in monkey models challenged with simian immunodeficiency virus (SIV).[1-3] Unfortunately, oral daily dosing and pre-exposure prophylaxis with tenofovir at a dose equivalent to that used in humans proved to only be partially protective against rectal SHIV transmission.[4]

HAART therapy involves the administration of a combination including at least three active compounds classified by the mode of operation as an NRTI, an NtRTIs, a non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitor, and an entry inhibitor. While HAART is effective in lowering retroviral titer in a host, concerns remain as to the long term toxicity and the retained potential to infect others. It is also unknown if initiating HAART therapy in a pre-exposure prophylactic regimen would be efficacious. As a result, society remains devoid of a pre-exposure prophylactic regimen to prevent an individual from developing self-propagating retrovirus infection subsequent to initial exposure.

Thus, there exists a need for a chemoprophylactic composition and dosing regimen effective in blocking early stage infection by retrovirus in a host founder cell population. There also exists a need for a chemoprophylactic composition formulated with a vehicle amenable to user compliance.

SUMMARY OF THE INVENTION

A process is provided for protecting a primate host from a self-replicating infection by an immunodeficiency retrovirus. Protection is achieved by administering to the primate host a combination of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to the immunodeficiency retrovirus. The administration is effective if provided in a single dose prior to the exposure. A regime of multiple temporally spaced doses prior to retroviral exposure is also effective in providing protection against an immunodeficiency retrovirus becoming self-replicating after infecting a primate host. A process for controlling retrovirus transmission within a population includes the administration to a subpopulation at high risk for contracting an immunodeficiency retroviral infection a combination of a pharmaceutically effective nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor prior to exposure to a source of immunodeficiency retrovirus so as to preclude the immunodeficiency retrovirus from becoming self-replicating in a member of the subpopulation.

A kit is also provided that includes at least one combination dose of a pharmaceutically effective amount of a nucleoside reverse transcriptase inhibitor and a pharmaceutically effective amount of a nucleotide reverse transcriptase inhibitor sufficient to protect a primate host from developing a self-replicating retroviral infection along with instructions for the administration of the at least one dose one prior to and optionally one additional dose subsequent to a potential exposure to an immunodeficiency retrovirus along with dosing modifications associated with subject characteristics and behaviors to further reduce the risk of contracting a self-replicating immunodeficiency retrovirus infection.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic depicting one study of the present invention for 4 groups of macaques in which all treated macaques received known antiretroviral medications 7 to 9 days prior to the first virus inoculation and continuing throughout the study with treated animals that remained uninfected throughout the 14 viral challenges receiving 28 additional days of post-exposure prophylactics.

FIG. **2** is a survival curve graph for macaque Groups 1-4 per FIG. **1**, as well as for animals receiving only tenofovir disoproxil fumarate (TDF).

FIG. **3** is a graph depicting a plot of viremia as a function of time for untreated controls (.) and breakthrough infections (●) where each point represents a mean viremia

observed. 0 time indicates peak plasma virus load observed in a given animal where the arrow bars denote standard error of the mean (SEM).

FIG. **4** depicts plots of infection dynamics as a function of time during the study per FIG. 1 with plots for animals coded as AG-80, AG-46, AII-04 and AG-07 corresponding to emtricitabine (FTC) treatment alone, or FTC plus TDF treatment (AI-54 and AG-81). The arrow indicates the first detectable antibody response. Grey circles indicate detectable M184V/I mutation: wild type sequences are shown in as black full circles. Open circles indicate the time points where no genotype was undertaken

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention has utility in protecting a primate host from self-propagating immunodeficiency virus infection. The use of a combination of antiretroviral agents as a prophylactic dosing regime is also provided for the manufacture of a medicament is provided for protection against a human immunodeficiency virus infection developing to a level of self-replicating infection. Retroviral transmission through most routes entails a new primate host receiving a small number of viral particles. Common routes of retrovirus transmission illustratively include sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, blood transfusions, birth canal exposure, breastfeeding, and transplacental contact between individuals. Through the administration of at least one nucleoside reverse transcriptase inhibitor (NRTI) and at least one nucleotide reverse transcriptase inhibitor (NtRTI) prior to a retrovirus exposure protection is provided against development of a self-replicating retroviral infection. As the aforementioned exposure routes are characterized by a small number of retrovirus particles being transferred to the new primate host, this initial phase of infection represents a window of opportunity to protect a host from infection. The inventive chemoprophylactic treatment is provided through a dosing regimen. A dosing regimen according to the present invention that provides retroviral protection to a host primate includes at least one single dose administered prior to initial retroviral exposure. An inventive dosing regimen also includes a course of multiple doses administered in advance of exposure to maintain a therapeutic level of NRTI and NtRTI agents in the primate host. The timing of the at least one dose prior to retroviral exposure is dictated by the pharmacokinetics of the NRTI and NtRTI components to assure the presence of a therapeutically effective amount of inventive composition for at least 20 hours subsequent to the exposure to the communicated small retroviral particle population. Multiple doses are administered according to the present invention at regular time intervals and amounts such as for example like formulated daily doses for a period of several days, weeks, or months; or are administered in advance of a likely exposure as a cluster of doses, with the amount of NRTI and NtRTI components in each dose being independent of the of amount of NRTI and NtRTI in other doses within the cluster. While most oral, topical, and parenteral existing versions of NRTIs and NtRTIs are fully absorbed and therapeutically active within 1 to 8 hours, it is appreciated that subcutaneous implants and long acting timed release formulations allow for a single dose to sustain therapeutically effective amounts of an inventive prophylactic composition for several days, weeks, or even months. Representative of sustained release compositions and implants are provided in the U.S. Pat. Nos. 4,122,129; 4,927,687; 4,996,047; 5,169,642; and 5,656,296.

The combination of NRTI and NtRTI compounds administered prophylactically according to the present invention are shown to provide a dose-dependent inhibition of HIV self-replicating infection and a therapeutically effective dosing primate host protection against self-replicating HIV infection is provided, even in response to multiple viral challenges. While the present invention is largely detailed with respect to HIV-1 as a prototypical infectious and pathogenic retrovirus, it is appreciated that other retroviruses owing to reliance on reverse transcription for replication are also protected against in a primate host according to the present invention.

As used herein, "protection" as used in the context of a host primate response to an immunodeficiency virus challenge is defined by the host primate being serologically negative and negative in response to a polymerase chain reaction (PCR) testing for viral genome.

As used herein, the term "retrovirus" is inclusive of any virus that utilizes reverse transcriptase in the viral replication cycle and therefore is susceptible to the antiviral activity of nucleoside or nucleotide analogs specifically inclusive of HIV (HIV-1 and HIV-2). HTLV-1, HTLV-2, HTLV-3, HTLV-4, and SIV. Also encompassed are viruses such as HBV that although not technically classified as retroviruses nonetheless utilize a reverse transcriptase and are therefore susceptible to the antiviral activity of nucleoside and/or nucleotide analogs.

As used herein a "primate host" is defined to include a monkey, baboon, chimpanzee, gorilla, and a human. Non-human primates are appreciated to themselves be susceptible to infection by retroviruses and in particular immunodeficiency viruses and represent well-established animal models as to human response with an appreciation that physiological differences often require different doses in milligrams per kilogram for a nonhuman primate animal model relative to a human.

The compositions of the present invention include administration in combination of an NRTI and NtRTI and are readily compounded by pharmaceutical composition with conventional pharmaceutically acceptable carriers or diluents. Additionally, pharmaceutically acceptable derivatives and prodrugs of active NRTIs and NtRTIs operative in the present invention include salts such as alkali metal salts; esters such as acetate, butyrate, octinoate, palmitate, chlorobenzoates, benzoates, C_1-C_6 benzoates, succinates, and mesylate; salts of such esters; and nitrile oxides. It is appreciated that other analogs of pharmaceutically active NRTIs or NtRTIs that provide within a primate host an active antiviral metabolite residue are also suitable as part of an inventive composition. A pharmaceutically acceptable carrier or diluent includes agents that are compatible with other ingredients of a dosage and not injurious to a primate host. The identity and process for compounding a combination of at least one NRTI and at least one NtRTI into a dosage form suitable for delivery by a route with administration by oral, rectal, topical, vaginal or parenteral routes of administration are provided in Remington's Science and Practice of Pharmacology, 20th Edition, Chapters 37-47, pages 681-929, where parenteral injection includes subcutaneous, intramuscular, intravenous, and intradermal injection.

As used herein the term "prodrug" is defined to include a compound that when administered to a primate host generates an active NRTI or NtRTI as a result of spontaneous reaction under physiological conditions, enzymatic cataly-

sis, metabolic clearance, or combinations thereof. An exemplary NtRTI prodrug currently FDA approved for HAART use is tenofovir disoproxil fumarate (TDF) and is detailed in U.S. Pat. No. 5,935,946.

The present invention provides an alternative to conventional retroviral therapy using HAART, in response to self-propagating HIV infection by protecting a primate host against the establishment of self-replicating retroviral infection that provides an indication for such therapy. Through prophylactic prior dosing with an inventive combination including at least one NRTI and one NtRTI, replication of the comparatively low number of viral particles received by a host primate is prevented.

To achieve protection against a primate host developing a retroviral self-replicating infection, at least one dosage of an NRTI and NtRTI is administered to the primate host prior to exposure to the retrovirus. Preferably, the at least one NRTI and at least one NtRTI are administered concurrently. More preferably, the combination of reverse transcriptase inhibitors is compounded into a single formulation.

The process of the present invention demonstrates protection against retroviral self-replicating infection through administration of even a single dosage administered prior to the retroviral exposure. Owing to the known pK rates of specific NRTIs and NtRTIs, a single dosage is administered to assure a therapeutically effective amount of NRTI and NtRTI persist in the primate host for a time of more than 12 hours after viral challenge. With conventional NRTI and NtRTI formulations, currently approved for HAART, preferably an inventive dose is administered within 12 hours prior to retroviral exposure and still more preferably often within 2 hours prior to retroviral exposure. The practice of the inventive process involving the administration of a single dosage in the hours proceeding a likely retroviral exposure is particularly advantageous in assuring compliant dosing in a human and also avoids side effects associated with a regular dosing regime and is particularly well suited for a human engaging in a sporadic behavior likely to bring the person into retroviral exposure. Preferably, an additional dose or doses of a combination of at least one NRTI and at least one NtRTIs is provided subsequent to the retroviral exposure event to assure adequate antiviral reverse transcriptase inhibitor concentration during and immediately subsequent to retroviral infection of the host founder cell population so as to preclude retroviral self-replication to assure NRTI and NtRTI incorporation into a replicating virus genome. Preferably, a dose of an inventive composition taken after retroviral exposure is administered within 24 hours subsequent to the exposure, and more preferably within 12 hours subsequent to the exposure.

Alternatively, an individual routinely subjected to retroviral exposure can be protected against the development of a self-replicating retroviral infection through administration of regular prophylactic doses of an inventive combination. As a result, an epidemiological advantage exists in controlling the outbreak and spread of a retrovirus within a population is provided through offering routine doses of an inventive composition prophylactically to high-risk persons such as sex workers and a short course prophylactic inventive composition to uninfected sex trade clientele.

It is appreciated that hybrid dosing regimes of an inventive composition are also operative herein and include multiple doses prior to retroviral exposure with multiple doses not being administered for a duration or with sufficient periodicity to arise to the level of a routine prophylactic regime.

The at least one nucleoside reverse transcriptase inhibitor has the attribute of interfering with in vivo viral replication. An NRTI operative in an inventive prophylactic process includes emtricitabine, lamivudine, zalcitabine, zidovudine, azidothymidine, didanosine, stavudine, abacavir; with the aforementioned specific NRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

An at least one nucleotide reverse transcriptase inhibitor (NRTI) present in an inventive composition to protect a primate from developing a self-replicating retroviral infection illustratively includes tenofovir, adefovir; 2',3'-dideoxy-3'-fluoroadenisine; 2',3'-dideoxy-3'-fluoroguanasine; 3'deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine with the aforementioned specific NtRTIs intended to include pharmaceutically acceptable salts, esters, ester salts, nitrile oxides, and prodrugs of any of the active agents.

Optionally, an inventive composition also includes within an inventive combination other antiretrovirals such as non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, and combinations thereof. Representative non-nucleoside reverse transcriptase inhibitors operative herein illustratively include delavirdine, efavirenz, nevirapine, and other diarylpyrimidine (DAPY) derivatives. Representative protease inhibitors operative herein illustratively include amprenavir, tipranavir, indinavir, saquinavir, lopinavir, ritonavir, fosamprenavir calcium, ritonavir, atazanavir sulfate nelfinavir mesylate, and combinations thereof. An entry inhibitor operative herein as an optional active ingredient in an inventive composition illustratively includes enfuvirtide, Schering C (Schering Plough), S-1360 (Shionogi), and BMS806 (Bristol Myers Squibb).

The dose of individual active components of an inventive prophylactic composition is administered to create a therapeutic concentration of the active composition at the situs of retrovirus initial founder cell population infection prior to viral exposure. It is appreciated that establishing a therapeutic concentration at the time of viral replication for a given NRTI, NtRTI or optional additional active agent in the target cells, includes factors for the therapeutic agent such as the route of administration, pharmacokinetics, absorption rate based on administration route, effects of food on oral absorption, in vivo distribution, metabolic pathways, elimination route, race, gender, and age of the subject, single dose incident side effects, long term administration side effects, and synergistic effects with co-administered active agents. Information related to these factors considered in dosing are available from the United States Food and Drug Administration (http://www.fda.gov/oashi/aids/virals.html). Preferably, NRTI and NtRTI prophylactic 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.

An inventive kit is provided that includes a 2-dose package of oral doses, such as tablets. In an exemplary embodiment of FDA approved NRTI and NtRTIs, each dose contains between 100 and 2500 milligrams (mg) of emtricitabine and between 100 and 2500 mg of TDF along with instructions to ingest the first dose approximately 1 to 8 hours prior to potential retroviral exposure and preferably about 2 hours there before, and a second dosage to be ingested 20 to 48 hours after potential retroviral exposure, preferably at about 22 hours thereafter. For an adult human, preferably each of the doses includes 200 mg of emtricitabine and 300 mg TDF. A non-human primate dose according to the present invention is typically higher on a mg per

kg animal body weight basis by a factor typically ranging from 2 to 10. Additional NRTIs, NtRTIs, NNRTIs, protease inhibitors or entry inhibitors are optionally provided in concert with either or both of these doses. The kit also includes instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the recipient (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. It is also appreciated that a carrier illustratively including a gel, jelly, cream, ointment, film, sponge, foam, suppository, vaginal ring or other delivery device is provided containing an NRTI such as emtricitabine, alone or in combination with an NtRTI such as tenofovir or TDF. The carrier is readily applied to mucosal tissue likely to be exposed to viral transmission as an added level of protection in concert with the oral doses.

An inventive kit is also provided that includes at least one NRTI and at least one NtRTI compounded as a gel, jelly, cream, ointment, film, sponge, foam, suppository, or applied to a vaginal ring or other like antiviral barrier. To prepare such a pharmaceutical compounded form, an effective amount of each of the active agents inclusive of at least one NRTI and NtRTI is combined in admixture with the pharmaceutically acceptable carrier or applied to a surface of the barrier. It is appreciated that the residence time of such a pharmaceutical composition is maintained at the site of administration through the inclusion of an optional bioadhesive that provides adhesion to mucosal tissue or the dermis. An inventive composition compounded for application to the dermis or mucosal tissue is provided along with instructions as to the timing of doses, contraindications, modifications associated with food ingestion, and additional behaviors that the person (synonymously described herein as a human primate host) can undertake to reduce the risk of retrovirus exposure and initial infection. Optionally, a kit containing an oral dosage is combined with a composition compounded for application to the dermis, rectal mucosa or vaginal mucosa so as to assure a therapeutically effective combination of NRTI and NtRTI at the mucosal point of retroviral entry associated with sexual exposure, as well as a therapeutically effective serum circulating quantity of prophylactic antiretrovirals.

The present invention is further detailed with respect to the following non-limiting examples. These examples are intended to provide exemplary specific embodiments of the present invention and are not intended to limit the scope of the appended claims.

EXAMPLES

Example 1

Antiretroviral Drugs and Doses

A dose of 22 mg/kg of tenofovir disoproxil fumarate (TDF) is given orally and 20 mg/kg of emtricitabine (FTC) given orally or subcutaneously to one group of adult male rhesus macaques. The 22 mg/kg TDF dose resulted in an area-under the plasma concentration-time curve over a 24 h interval (AUC) of 4.49 μg×hr/ml which was similar to the value of 5.02 μg×hr/ml observed in human receiving 300 mg of TDF. The dose of 20 mg/kg of FTC resulted in an AUC value (11 μg×hr/ml), also similar to that observed in humans receiving 200 mg of FTC orally (10.0±3.12 μg×hr/ml)[6]. Subcutaneous administration of FTC results in plasma FTC levels comparable to those achieved during oral administration, indicating a high FTC absorption in rhesus macaques.

Oral administration of FTC and TDF to macaques is by mixing the drug powders with peanut butter or fruit. Macaques are observed to ensure ingestion.

Example 2

Virus Inoculations

A chimeric envelope $SHIV_{SF162P3}$ isolate is used to inoculate the macaques. $SHIV_{SF162P3}$ is a construct that contains the tat, rev, and env coding regions of $HIV\text{-}1_{SF162}$ in a background of SIVmac239. This isolate was obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.[7,8] Virus exposures are performed 2 hours after drug treatment, and involved non-traumatic inoculation of 1 mL of $SHIV_{SF162P3}$ ($10\ TCID_{50}$ or 7.5×10^6 viral RNA copies) into the rectal vault via a sterile gastric feeding tube.[9] Anesthetized macaques remained recumbent for at least 15 min after each intrarectal inoculation.

Example 3

SHIV Viral Load Assay

Plasma RNA is quantified using a real-time PCR assay as previously described.[5] This assay has a sensitivity of detection of 50 RNA copies/ml or 10 copies of a pVp1 plasmid carrying the SIVmac239 RT gene. HIV-1 RNA is extracted from 1 mL of plasma using the NucliSens extraction method (bioMerieux). A known amount of virus particles (3×10^5) from an HIV-1 CM240 virus stock is added to each sample prior to extraction to control for the efficiency of extraction. Reverse transcription is performed using 10 microliters (μl) of extracted RNA and the 2-step TaqMan Gold reverse-transcriptase (RT) -PCR kit (Applied Biosystems) according to the manufacturer's instructions. PCR reactions are performed as described using an ABI 7000 Gene Detection System (Applied Biosystems). Virus loads are calculated from a standard curve generated with known amount of virus particles. All primers and probes used for SIVmac239 and HIV-1 CM240 have been reported elsewhere.[5] HIV-1 CM240 is obtained from the National Institutes of Health (NIH) AIDS Research and Reference Reagent Program.

Example 4

Detection of Genotypic Resistance to FTC and Tenofovir

Emergence of FTC and tenofovir resistance is monitored by sequence analysis of SIV RT (551 bp; amino acids 52 to 234) and by a more sensitive allele-specific real-time PCR method for the K65R and M184V mutations. Sequence analysis was done from plasma viruses using an RT-PCR procedure as previously described.[5] The Vector NTI program (Version 7, 2001) is used to analyze the data and to determine deduced amino-acid sequences. Detection of low frequency of K65R and M184V mutants in plasma by real-time PCR is performed as previously described.[10] These assays have a detection limit of 0.4% of K65R and 0.6% of M184V cloned sequences in a background of wild type plasmid.

Example 5

Virus-Specific Antibody Responses

Virus-specific serologic responses (IgG and IgM) are measured using a synthetic-peptide EIA (Genetic Systems HIV-1/HIV-2) assay.

Example 6

Statistical Methods

The exact log-rank test is used for a discrete-time survival analysis of the treatment and control groups, with use of the number of inoculations as the time variable. The Cox proportional hazards model is used to estimate the relative hazard ratio (HR). Percent protection is calculated from the HR value using the formula: (1-1/HR)×100. All statistical analyses for calculation of the efficacy of the different interventions are performed using SAS software (version 9.1; SAS Institute) and StatXact software (version 6.3; Cytel).

Example 7

Routine Dosing Experimental Design

Macaques are exposed rectally once weekly for up to 14 weeks to SHIV162p3 which contains an R5 tropic HIV-1 envelope that resembles naturally transmitted viruses. The SHIV162p3 challenge dose is 10 $TCID_{50}$ or 7.6×10^5 RNA copies which is similar to HIV-1 RNA levels in semen during acute infection in humans.[11] Virus exposures are terminated when a macaque became infected. FIG. **1** shows the study design and the interventions evaluated in each group of macaques. Three prophylactic drug treatments of increasing drug potency are each given once daily to a group of six macaques. Animals in Group 1 were treated subcutaneously with 20 mg/kg of FTC alone. Animals in Group 2 received orally a combination of FTC (20 mg/kg) and TDF (22 mg/kg). Animals in Group 3 had the most protective treatment with subcutaneous 20 mg/kg of FTC and a 22 mg/kg of tenofovir (PMPA). The rate of infection in each group is compared with that seen in 18 untreated control macaques (9 real time and 9 historical controls).

All treated macaques received the corresponding drugs 7 to 9 days prior to the first virus inoculation to achieve steady-state plasma levels. Treated animals that remained uninfected during the 14 challenges received 28 days of post-exposure prophylaxis after the last challenge. Protection was defined as absence of persistent viremia and seroconversion. Treated animals that became infected continued treatment for an average of 21 weeks (range 13 to 29) to monitor for plasma viremia and drug resistance development.

Example 8

Survival Curves

FIG. **2** shows the survival curves observed for each group of animals per Example 7. Data with TDF (20 mg/kg) is also provided for comparison. Untreated macaques are infected after a median of 2 rectal exposures (mean 4). The majority of the animals (13/18 or 72%) are infected during the first 4 challenges (median 2): 4 (22%) are infected between exposures 8 and 14 (mean 10), and only 1 (6%) remained uninfected after 14 exposures. The median 2 exposures for infection in controls suggests that an animal receiving prophylactic treatment and remaining uninfected after 14 virus challenges would have been protected against a median of 7 rounds of transmissions. Treatments of Groups 1-3 are all protective to a degree with a clear dose-response relationship being observed. All 6 macaques in Group 3 that received the most potent inventive composition remained uninfected demonstrating that full protection against repeated challenges is possible. Of the 6 macaques in Group 2, 4 were protected and only 2 (animal reference numbers AI-54 and AG-81) became infected at exposures 9 and 12. Compared to controls, infection in this group is reduced by 7.8-fold (Cox proportional hazard ratio [HR] 7.8, p 0.0075). Infection in both animals is significantly delayed compared to the untreated controls (p 0.0004). These 2 macaques became seropositive 2 weeks after the first detectable viral RNA in plasma and both were proviral DNA positive at weeks 10 and 12, respectively. Of the 6 macaques in Group 1 receiving FTC only, 2 remained protected after 14 exposures and 4 had the first detectable viral RNA at exposures 5 (AG-80), 10 (AG-46), 12 (AH-04), and 13 (AG-07), respectively. Survival analysis showed a statistically significant difference from untreated controls (p=0.004). Compared to controls, infection is reduced 3.8-fold macaques (Cox proportional hazard ratio [HR]=3.8, p 0.021). Infection in these 4animals is also confirmed by PCR amplification of proviral DNA from PBMC's and by serology; antibody responses are detectable 3, 1, 2, and 6 weeks after the first detectable RNA, respectively. FIG. **2** also shows that the protection achieved with FTC alone was higher than that previously seen in 4 animals receiving TDF,[5] consistent with the slightly higher potency of FTC, although the difference was not statistically significant (p 0.5).

Example 9

Prophylactic Breakthrough Infections and Drug Resistance Emergence

Since the dynamics of breakthrough infections that occur during inventive prophylaxis and drug resistance emergence are unknown, the 6 infected animals from Groups 1 and 2 are followed under continued drug treatment. FIG. **3** compares the virus load kinetics in the 6 breakthrough infections with those in 12 untreated macaques that had sufficient follow-up samples. The mean peak viremia in the 6 treated macaques was 4.9 ± 0.5 $\log_{10}$ RNA copies/ml, 2.0 $\log_{10}$ lower than in untreated controls (6.9 ± 0.3 $\log_{10}$ RNA). FIG. **3** also shows that such differences in viremia were maintained up to week 11 as indicated by similar rate of virus load decline seen in the two groups of animals (-0.23 ± 0.02 $\log_{10}$/week in treated vs. -0.29 ± 0.02 $\log_{10}$/week in untreated controls). The individual virus load kinetics in the 6 breakthrough infections are shown in FIG. **4**. Three FTC (AG-80, AH-04, and AG-07) and one of the FTC/TDF (AG-81) failures had undetectable virus loads 3, 4, 7, and 11 weeks after the peak in viremia, respectively; viremia in these animals remained consistently low or undetectable for up to 20 weeks. In contrast, all 12 untreated macaques had detectable virus loads during a median follow-up period of 7 weeks (range 5-36 weeks). The arrow in FIG. **4** denotes the first detectable antibody response. Grey circles indicate detectable M184V/I mutation; wild type sequences are shown in black full circles. Open circles are provided for data points not genotyped.

Drug resistance testing showed that wild type virus initiated all 6 breakthrough infections in Groups 1 and 2 reflecting residual virus replication in target cells not protected by drugs (FIG. 4). Four animals had no evidence of drug resistance despite extended treatment (median 23 weeks). Only 2 animals had detectable M184V (AG-46, FTC-treated) or M1841 (AI-54 FTC/TDF-treated) mutations associated with FTC resistance at week 4 and 10, respectively. The tenofovir-associated K65R mutation is not detected in the 2 Group 2 animals receiving FTC/TDF. FIG. 4 also shows that the 2 macaques that selected M184V/I had the highest peak viremias. Without intending to be bound to a particular theory, it is hypothesized that more virus replication in these animals may have facilitated drug resistance selection. Reductions in acute viremia are proposed to contribute at a population level to a decrease in virus transmissibility.

Example 10

Single Dosing

The process of Example 7 is repeated in Group 3 with drugs only being administered 2 hours prior to and 22 hours subsequent to each inoculation. The resultant survival curves are comparable to those detailed in Example 8.

Example 11

Single Dosing with Suppository

A group of 6 macaques received the drug treatment of Group 3 per Example 7 in the form of a gel inserted rectally containing 300 mg of tenofovir and 300 mg lamuvidine (3-TC) 1 hour before viral inoculation with observation to assure that the suppository is not voided. The gel is formed by compounding tenofovir and 3-TC in 2% by weight hydroxyethyl cellulose (HEC)-based gel in both a vaginal formulation (pH 4.5) and rectal formulation (pH 6.5) containing (w/v) 3% tenofovir, and 3% 3-TC. The gels are stable at room temperature for at least five months with no loss in activity; and gels retained full activity at both pH 4.5 and pH 6.5 at levels equivalent to those observed for tenofovir and 3-TC preparations in water. Using an MT4/MTT phenotypic assay, all gels were tested for activity against wild-type HIV-1_{IIIB}, and resistant HIV-1 viruses containing the K65R or M184V mutations. No significant cytotoxicity is seen in the cervical explant model.

Viral protection of the macaques is maintained throughout the study.

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Patent documents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. These documents and publications are incorporated herein by reference to the same extent as if each individual document or publication was specifically and individually incorporated herein by reference.

The foregoing description is illustrative of particular embodiments of the invention, but is not meant to be a limitation upon the practice thereof. The following claims, including all equivalents thereof, are intended to define the scope of the invention.

The invention claimed is:

1. 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 the primate host a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir prodrug,

wherein the combination is administered orally prior to the exposure of the primate host to the immunodeficiency retrovirus,

thereby protecting the primate host from infection with the immunodeficiency retrovirus.

2. The process of claim **1**, wherein selecting a primate host comprises selecting an adult human not infected with the immunodeficiency retrovirus.

3. The process of claim **2**, wherein the adult human is a male.

4. The process of claim **2**, wherein the pharmaceutically effective amount of emtricitabine and the pharmaceutically effective amount of tenofovir or the tenofovir prodrug, are administered directly to the human in a combined single dosage formulation.

5. The process of claim **2**, wherein the immunodeficiency retrovirus is a human immunodeficiency virus.

6. The process of claim **5**, wherein a human immunodeficiency virus (HIV) is HIV-1.

7. The process of claim **1**, wherein the combination is administered as preexposure prophylactic treatment prior to rectal and/or vaginal exposure of the primate host to the immunodeficiency retrovirus.

8. The process of claim **1**, comprising administering 200 milligrams (mg) of emtricitabine to the primate host.

9. The process of claim **1**, wherein the combination s administered daily for several days, weeks or months.

10. The process of claim **9**, wherein 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.

11. The process of claim **1**, wherein administration of the combination results in a absence of persistent viremia and seroconversion of the primate host.

12. A process for inhibiting establishment of a human immunodeficiency virus self-replicating infection of human immunodeficiency virus infection in a human, comprising:

(a) selecting an uninfected human that does not have the self-replicating infection; and

(b) administering to the uninfected human a combination comprising:

i. a pharmaceutically effective amount of emtricitabine; and

ii. a pharmaceutically effective amount of tenofovir or a tenofovir prodrug;

thereby inhibiting the establishment of the self-replicating infection with the immunodeficiency virus in the human, wherein the combination is administered prior to potential exposure the human to the human immunodeficiency retrovirus.

13. The process of claim **12**, wherein combination is compounded into a single formulation.

14. The process of claim **13**, wherein the single formulation is administered daily for several days, weeks or months both before and after an exposure of the primate host to the immunodeficiency retrovirus.

15. The process of claim **12**, wherein an inhibition of infection in the host is determined by an absence of persistent viremia and seroconversion in the human following the exposure to the immunodeficiency retrovirus.

16. The process of claim **12**, wherein:

(i) the pharmaceutically effective amount of emtricitabine; and

(ii) the pharmaceutically effective amount of tenofovir or the tenoforvir prodrug; are formulated in a single tablet.

17. The process of claim **12**, wherein the potential exposure to the human immunodeficiency retrovirus comprises sexual intercourse, medical worker skin puncture inoculation, hypodermic needle sharing, or blood transfusion.

18. The process of claim **12**, wherein the combination comprises the tenofovir prodrug.

19. The process of claim **1**, wherein the combination comprises the tenofovir prodrug.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,335,423 B2
APPLICATION NO. : 15/913750
DATED : July 2, 2019
INVENTOR(S) : Heneine et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

Column 10, Line 27, "4animals" should read --4 animals--.

In the Claims

Claim 9, Column 13, Line 33, "combination s" should read --combination is--.

Claim 11, Column 13, Line 40, "a absence" should read --an absence--.

Claim 12, Column 14, Line 16, "exposure the human" should read --exposure of the human--.

Signed and Sealed this
Second Day of March, 2021

Drew Hirshfeld
Performing the Functions and Duties of the
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET - Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. ED 490297095 US

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☐ *Additional inventors are being named on the* _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

METHODS AND COMPOSITIONS FOR CHEMOPROPHYLAXIS

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ENCLOSED APPLICATION PARTS ***(check all that apply)***

☐ Application Data Sheet. See 37 CFR 1.76

☒ Specification *Number of Pages* **20**

☐ Drawing(s) *Number of Sheets*

Total # of sheets **20**

☐ CD(s), Number of CDs

☐ Other (specify)

= Application Size Fee **$0.00**

Fees Due: Filing Fee of $200. If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is $250 for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

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This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Page 2 of 2

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Centers for Disease Control and Prevention

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SIGNATURE Sumita Chowdhury-Ghosh Date **February 3, 2006**

TYPED or PRINTED NAME **Sumita Chowdhury-Ghosh** REGISTRATION NO. *(if appropriate)* **50,476**

TELEPHONE **770-488-8612** Docket Number: **I-022-06US1P**

020306 04/77

Doc Code:

PTO/SB/17 (01-06)
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U.S. PTO

Fees pursuant to the Consolidated Appropriatons Act, 2005 (H.R. 4818).

FEE TRANSMITTAL for FY 2006

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) **$200.00**

Complete if Known	
Application Number	**To be assigned**
Filing Date	**February 3, 2006**
First Named Inventor	**Walid HENEINE**
Examiner Name	**N/A**
Art Unit	**N/A**
Attorney Docket No.	**I-022-06US1P**

METHOD OF PAYMENT (check all that apply)

☐ Check ☒ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Deposit Account Number: _____ Deposit Account Name: _____

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

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FEE CALCULATION (All the fees below are due upon filing or may be subject to a surcharge.)

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	$200.00

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
17 - 20 or HP =	0 x	$50.00 =	$0.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
5 - 3 or HP =	x	$200.00 =	$0.00

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims		
	Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listing under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
20 - 100 =	0 / 50	0 (round up to a whole	x $250.00 =	$0.00

4. OTHER FEE(S)

	Fee Paid ($)
Non-English specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge):	

SUBMITTED BY

Signature	Sumita Chowdhury-Ghosh	Registration No. (Attorney/Agent)	50,476	Telephone	770-488-8612
Name (Print/Type)	**Sumita Chowdhury-Ghosh**			Date	**February 3, 2006**

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): HENEINE et al.			Docket No. I-022-06US1P	
Application No. To be assigned	Filing Date February 3, 2006	Examiner N/A	Customer No. 52567	Group Art Unit N/A

Invention: METHODS AND COMPOSITIONS FOR CHEMOPROPHYLAXIS

I hereby certify that the following correspondence:

Provisional Patent Application (20 sheets), Provisional Patent Application Cover Sheet, Credit Card Payment Form, Fee Transmittal, Acknowledgment Postcard

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

February 3, 2006
(Date)

Sumita Chowdhury-Ghosh
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P06A/REV03

Prevention of rectal SHIV transmission in macaques by tenofovir/FTC combination

J. Gerardo García-Lerma, Ronald Otten, Shoukat Qari, Eddie Jackson, Wei Luo, Caryn Kim, Debra Adams, Michael Monsour, Raymond Schinazi, Robert Janssen, Thomas Folks, Walid Heneine

Background: Chemoprophylaxis with antiretrovirals as a strategy to prevent the transmission of human immunodeficiency virus (HIV) is being explored, although information on the most effective antiretroviral intervention is not yet known. Available data on tenofovir using macaque models of simian HIV (SHIV) mucosal infection suggest that tenofovir is not sufficiently protective at concentrations equivalent to those currently used in humans. Here, we investigated whether tenofovir/5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine(FTC, emtricitabine) combination protects macaques from rectal SHIV challenge, and whether this protection is sustained during repeated virus exposures.

Methods: One group of six Rhesus macaques was injected subcutaneously with 22mg tenofovir/20mg FTC per kg once daily. The FTC dose is comparable to that approved for humans. Six control animals did not receive any antiretroviral treatment. All animals were subjected to weekly rectal exposures with a low dose of $SHIV_{SF162p3}$ (10 $TCID_{50}$; $3.8x10^5$ virus particles) which expresses an R5 tropic HIV-1 envelope that resembles naturally transmitted HIV-1 strains. Infection was monitored by serology and PCR amplification of SHIV gag and pol sequences from plasma and peripheral blood lymphocytes, respectively. Historic data on control macaques using this repeat exposure model shows that four virus challenges infect ~75% of the animals.

Results: Four of six controls (67%) became infected after four challenges (median = 2.5; range = 2-4). In contrast, all six animals treated with tenofovir/FTC were fully protected. After ten additional virus challenges, one of two remaining controls became infected while all six tenofovir/FTC-treated animals remained uninfected.

Conclusions: Tenofovir/FTC combination provides a high level of protection against repeated virus challenges, demonstrating that chemoprophylaxis with potent antiretrovirals is an effective strategy for preventing sexual HIV transmission.

Prevention of Rectal SHIV Transmission in Macaques by Tenofovir/FTC Combination

Walid Heneine

Laboratory Branch
Division of HIV/AIDS Prevention

Introduction

- In the absence of an effective vaccine, chemoprophylaxis with antiretrovirals has considerable potential for preventing HIV-1 transmission
- Macaque models show that tenofovir can provide substantial protection against parenteral or mucosal virus exposures
- However, this protection may be reduced at lower drug doses equivalent to those used in humans
- Current human trials with tenofovir will ultimately determine the efficacy of this intervention

Introduction

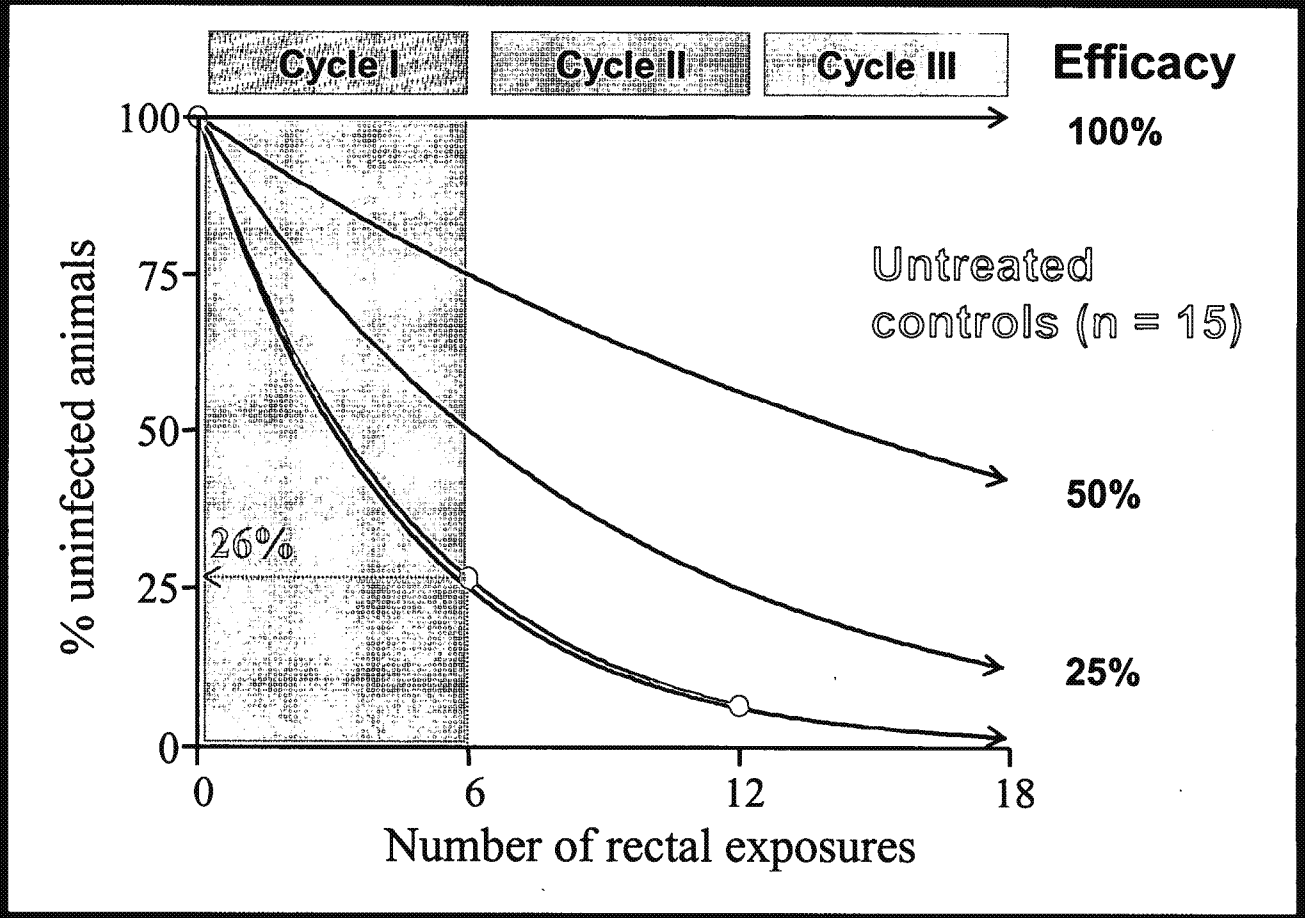
- Many potent antiretrovirals with favorable safety and pharmacodynamic profiles are now available and are good candidates for chemoprophylaxis
- Can these drugs fully protect against sexual transmission?
- What is the relationship between drug potency and protection?
- Higher drug potency provides more protection?
- We determined whether the increased potency in a combination of 2 RT inhibitors, tenofovir and FTC, protects macaques from repeated virus exposures

Materials and Methods

- Six male Rhesus macaques injected subcutaneously with tenofovir 22 mg/kg and FTC 20 mg/kg once daily
- Six controls received no drug treatment
- Repeated rectal exposures once weekly with SHIV162p3 that contains an HIV-1 R5 env; 14 total virus exposures
- Virus inoculum: 10 TCID ($3.8\ 10^5$ virus particles equivalent)
- Infection was monitored by serology, RT-PCR of plasma and proviral PCR of PBMC
- Animals considered protected if seronegative and PCR negative

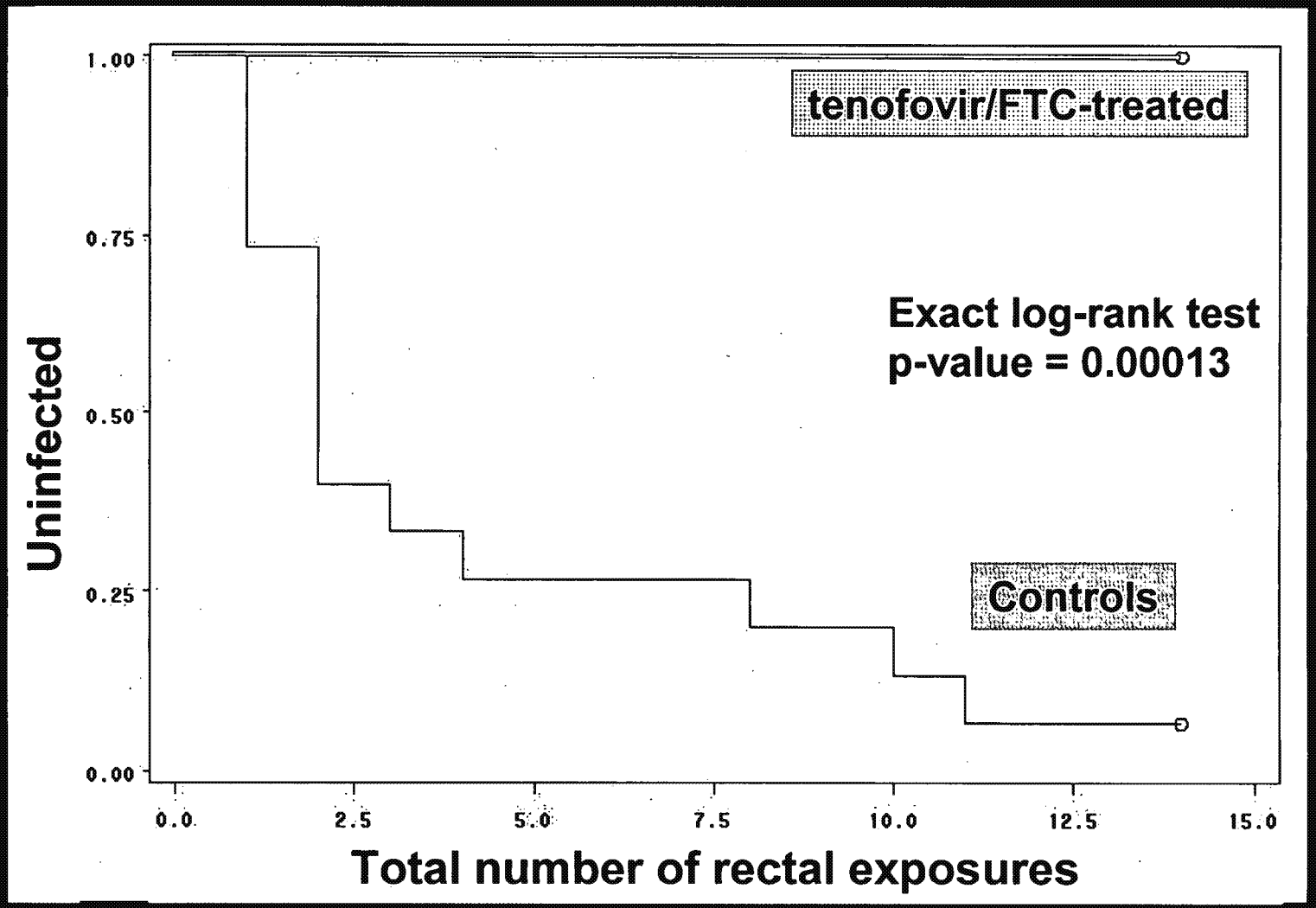
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Repeat low-dose model



Controls, median 2 exposures (range 1-11)

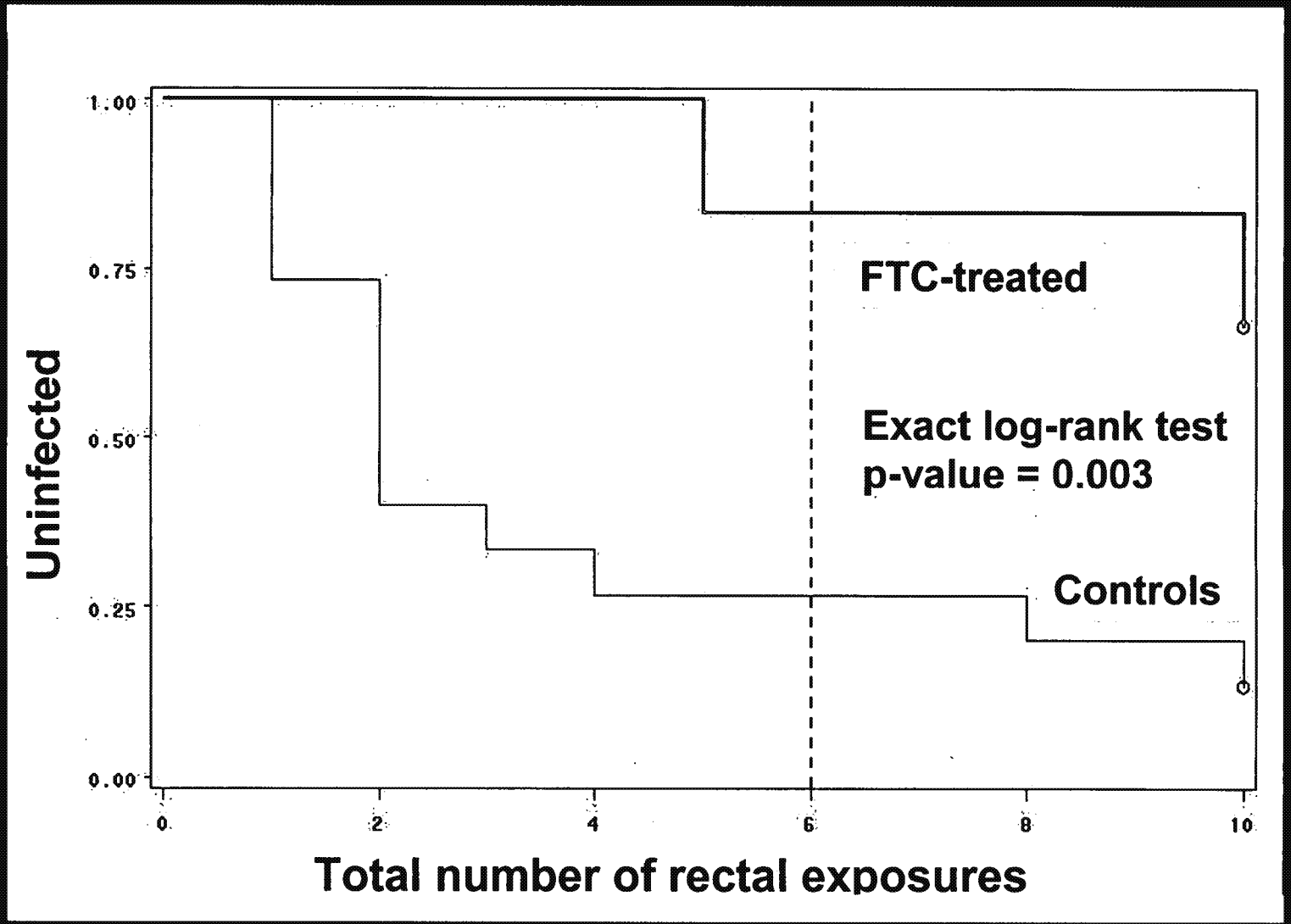
Prevention of rectal SHIV transmission in macaques by tenofovir/FTC combination



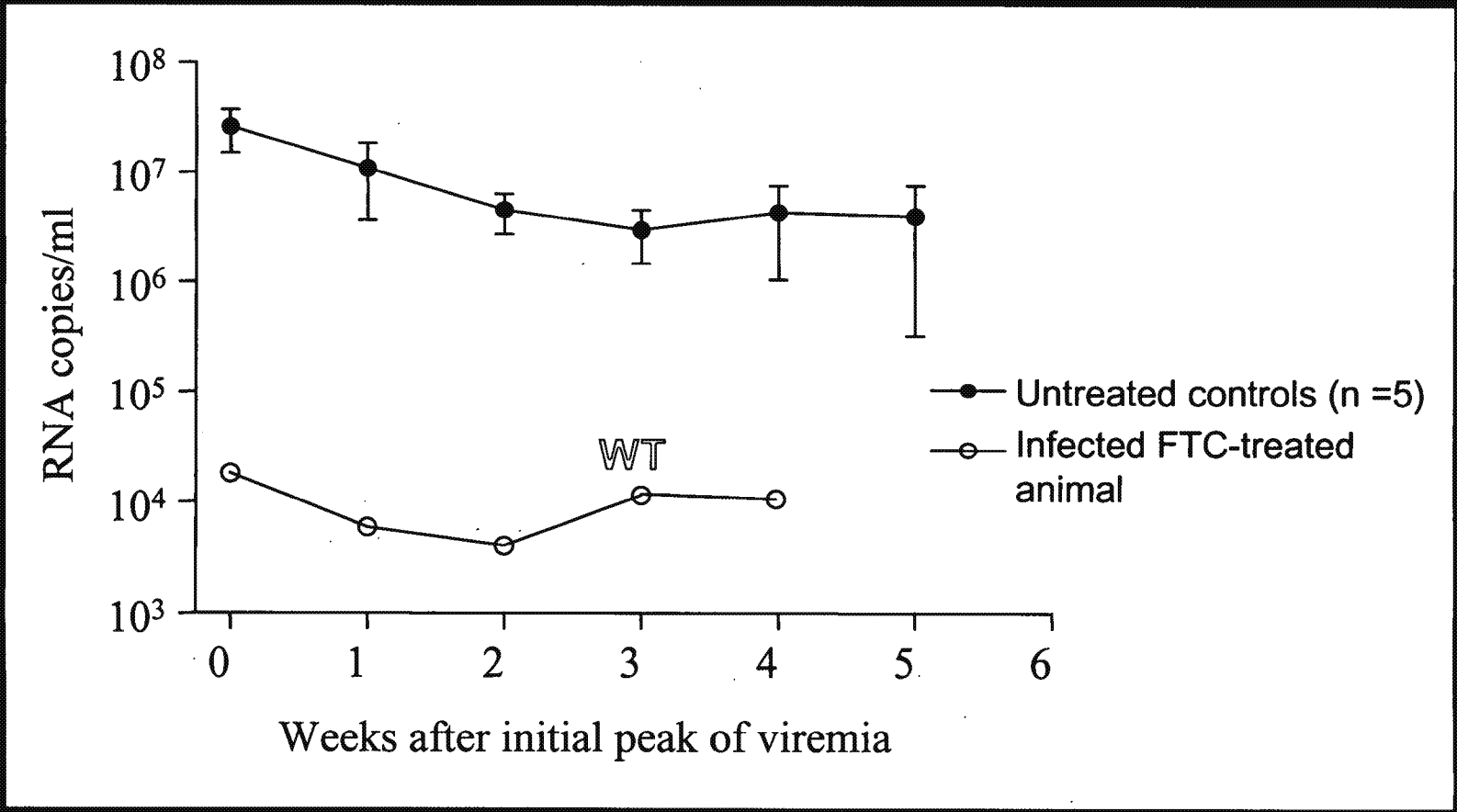
Chemoprophylaxis with FTC only

- How much FTC (Emtricitabine, Emtriva) contributes to the observed protection?
- FTC is very potent (~1.8 decrease in virus load)
- Well tolerated, good safety profile, once daily dosing, long intracellular half-life (40 h)
- Pharmacokinetic analysis suggests that 20 mg/kg/day in rhesus macaques is equivalent to the dose used in humans
- Evaluated protection by FTC in six Rhesus macaques

High level protection of rectal SHIV transmission by FTC alone



Decreased peak viremia and viral set point in an infected FTC-treated macaque



Summary and Conclusions

- Tenofovir/FTC combination protected all 6 treated animals from infection after 14 repeated rectal SHIV exposures
- Treated animals remained uninfected despite receiving seven times more exposures than controls (median exposures to infect controls is 2)
- Data suggest that chemoprophylaxis with a potent antiretroviral drug combination can be highly effective in preventing sexual HIV transmission
- The observed protection by tenofovir and FTC may not reflect that of Truvada, because a higher dose of tenofovir was used

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Summary and Conclusions

- Ongoing study suggests that FTC alone at a dose similar to that used in humans shows a predicted efficacy of ~75%.
- In the Cox proportional hazards model control monkeys are 5.7 times more likely to become infected than treated monkeys (p-value is 0.024)
- Single-drug prophylaxis with FTC appears very effective. Conclusive data when study is completed.
- Adding tenofovir to FTC at a dosing similar to that in Truvada may enhance further the protection
- Drug potency matters for preventing sexual infection by chemoprophylaxis

Acknowledgments

CDC

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Eddie Jackson
Wei Luo
Caryn Kim
Debra Adams
Michael Monsour
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Raymond F Schinazi

Gilead

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UC Davis

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current October 2005

Drugs Used in the Treatment of HIV Infection

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Combivir	lamivudine and zidovudine	GlaxoSmithKline	27-Sep-97	3.9 months
Emtriva	FTC, emtricitabine	Gilead Sciences	02-Jul-03	10 months
Epivir	lamivudine, 3TC	GlaxoSmithKline	17-Nov-95	4.4 months
Epzicom	abacavir/ lamivudine	GlaxoSmithKline	02-Aug-04	10 months
Hivid	zalcitabine, ddC, dideoxycytidine	Hoffmann-La Roche	19-Jun-92	7.6 months
Retrovir	zidovudine, AZT, azidothymidine, ZDV	GlaxoSmithKline	19-Mar-87	3.5 months
Trizivir	abacavir, zidovudine, and lamivudine	GlaxoSmithKline	14-Nov-00	10.9 months
Truvada	tenofovir disoproxil/emtricitabine	Gilead Sciences, Inc.	02-Aug-04	5 months
Videx EC	enteric coated didanosine	Bristol Myers-Squibb	31-Oct-00	9 months
Videx	didanosine, ddI, dideoxyinosine	Bristol Myers-Squibb	9-Oct-91	6 months
Viread	tenofovir disoproxil fumarate	Gilead	26-Oct-01	5.9 months
Zerit	stavudine, d4T	Bristol Myers-Squibb	24-Jun-94	5.9 months
Ziagen	abacavir	GlaxoSmithKline	17-Dec-98	5.8 months

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Rescriptor	delavirdine, DLV	Pfizer	4-Apr-97	8.7 months
Sustiva	efavirenz	Bristol Myers-Squibb	17-Sep-98	3.2 months
Viramune	nevirapine, BI-RG-587	Boehringer Ingelheim	21-Jun-96	3.9 months

Protease Inhibitors (PIs)

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Agenerase	amprenavir	GlaxoSmithKline	15-Apr-99	6 months
Aptivus	tipranavir	Boehringer Ingelheim	22-Jun-05	6 months
Crixivan	indinavir, IDV, MK-639	Merck	13-Mar-96	1.4 months
Fortovase	saquinavir	Hoffmann-La Roche	7-Nov-97	5.9 months
Invirase	saquinavir mesylate, SQV	Hoffmann-La Roche	6-Dec-95	3.2 months
Kaletra	lopinavir and ritonavir	Abbott Laboratories	15-Sep-00	3.5 months
Lexiva	Fosamprenavir Calcium	GlaxoSmithKline	20-Oct-03	10 months
Norvir	ritonavir, ABT-538	Abbott Laboratories	1-Mar-96	2.3 months
Reyataz	atazanavir sulfate	Bristol-Myers Squibb	20-Jun-03	6 months
Viracept	nelfinavir mesylate, NFV	Agouron Pharmaceuticals	14-Mar-97	2.6 months

Fusion Inhibitors

Brand Name	Generic Name	Manufacturer Name	Approval Date	Time to Approval
Fuzeon	enfuvirtide, T-20	Hoffmann-La Roche & Trimeris	13-Mar-03	6 months

Generic drugs used in the Treatment of HIV Infection

Drugs Used in the Treatment of Pediatric HIV Infection

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current October 2005

Generic Drugs Used in the Treatment of HIV Infection

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name	Manufacturer Name	Approval Date	Time to Approv
didanosine (ddI) Delayed Release capsules	Barr Laboratories, Inc.	03-Dec-04	6 month
Oral Solution -zidovudine, AZT, azidothymidine, ZDV (Pediatric formulation)	Aurobindo Pharma Limited	19-Sep-05	6 month
zidovudine, AZT, azidothymidine, ZDV	Aurobindo Pharma Limited	19-Sep-05	10 mon
zidovudine, AZT, azidothymidine, ZDV	Ranbaxy Laboratories Limited	19-Sep-05	11 mon
zidovudine, AZT, azidothymidine, ZDV	Roxane Laboratories	19-Sep-05	24 mon

Drugs Used in the Treatment of HIV Infection (approved innovator products)

Drugs Used in the Treatment of Pediatric HIV Infection (approved innovator products)

Drugs Used in the Treatment of Pediatric HIV Infection

Brand Name	Generic Name	Manufacturer	Adult Approval Date	Pediatric Approval Date
Agenerase	amprenavir	GlaxoSmithKline	15-Apr-99	15-Apr-99
Combivir	zidovudine and lamivudine	GlaxoSmithKline	26-Sep-97	no pediatric labeling*
Crixivan	indinavir	Merck	13-Mar-96	no pediatric labeling*
Emtriva	emtricitabine	Gilead Sciences	02-Jul-03	09-28-05
Epivir	lamivudine, 3TC	GlaxoSmithKline	17-Nov-95	17-Nov-95
Fortovase	saquinavir	Roche	7-Nov-97	no pediatric labeling*
Hivid	zalcitabine, ddC	Roche	19-Jun-92	no pediatric labeling*
Invirase	saquinavir	Roche	6-Dec-95	no pediatric labeling*
Kaletra	lopinavir, ritonavir	Abbott Laboratories	15-Sep-00	15-Sep-00
Norvir	ritonavir	Abbott Laboratories	1-Mar-96	14-Mar-97
Rescriptor	delavirdine	Pfizer	4-Apr-97	no pediatric labeling*
Retrovir	zidovudine, AZT, ZDU	GlaxoSmithKline	19-Mar-87	1-May-90
Sustiva	efavirenz	Bristol Myers-Squibb	21-Sep-98	21-Sep-98
Videx	didanosine, ddI	Bristol Myers-Squibb	9-Oct-91	9-Oct-91
Viracept	nelfinavir	Agouron Pharmaceuticals	14-Mar-97	14-Mar-97
Viramune	nevirapine	Boehringer Ingelheim	21-Jun-96	11-Sep-98
Viread	tenofovir disoproxil fumarate	Gilead	26-Oct-01	no pediatric labeling*
Zerit	stavudine, d4T	Bristol Myers-Squibb	24-Jun-94	6-Sep-96
Ziagen	abacavir	GlaxoSmithKline	17-Dec-98	17-Dec-98

* "While some of these drugs may, in practice, be used in the treatment of children of various ages, the sponsors have not submitted data to support a labeled pediatric indication at this time."

Generic Drugs Used in the Treatment of HIV Infection

Drugs Used in the Treatment of HIV Infection

HIV/AIDS Home Page
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FDA Office of Special Health Issues

We claim:

1. A composition for the prevention of HIV transmission comprising a plurality of antiretroviral compounds.

2. The composition of Claim 1 further comprising derivatives of said plurality of antiretroviral compounds.

3. A composition for the prevention of HIV transmission comprising a plurality of antiretroviral compounds in sufficient amounts to prevent viral infection in a subject.

4. The composition of Claim 1, wherein at least one of the plurality of antiretroviral compounds is selected from the group consisting of tenofovir, FTC, United States Food and Drug Administration approved drugs used in the treatment of HIV infection, generic drugs used in the treatment of HIV infection, United States Food and Drug Administration approved drugs used in the treatment of pediatric HIV infection and derivatives thereof.

5. The composition of Claim 1, wherein the plurality of antiretroviral compounds are in particle form and tableted with pharmaceutically acceptable carriers or tableting agents.

6. The composition of Claim 1, wherein the plurality of antiretroviral compounds are in combination with a pharmaceutically acceptable liquid carrier.

7. The composition of Claim 1, wherein the plurality of antiretroviral compounds are in combination with a pharmaceutically acceptable gel carrier.

8. A method of preventing HIV transmission in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising a plurality of antiretroviral compounds in sufficient amounts to prevent viral infection in the subject.

9. The method of Claim 8, further comprising derivatives of said plurality of antiretroviral compounds.

10. The method of Claim 8, wherein the wherein at least one of the plurality of antiretroviral compounds is selected from the group consisting of tenofovir, FTC United States Food and Drug Administration approved drugs used in the treatment of HIV infection, generic drugs used in the treatment of HIV infection, United States Food and Drug Administration approved drugs used in the treatment of pediatric HIV infection and derivatives thereof.

11. The method of Claim 8, wherein the plurality of antiretroviral compounds are in particle form and tableted with pharmaceutically acceptable carriers or tableting agents.

12. The method of Claim 8, wherein the plurality of antiretroviral compounds are in combination with a pharmaceutically acceptable liquid carrier.

13. The method of Claim 8, wherein the plurality of antiretroviral compounds are administered at least once.

14. The method of Claim 8, wherein administration of the plurality of antiretroviral compounds is selected from the group consisting of topical, oral and injectable.

15. A method of antiviral chemoprophylaxis, comprising administering to the subject a therapeutically effective amount of a composition comprising a plurality of antiviral compounds in sufficient amounts to prevent viral infection in the subject.

16. A composition for the prevention of viral transmission comprising a plurality of antiviral compounds.

17. A method of preventing HIV transmission in a subject, comprising administering to the subject a chemoprophylatically effective amount of a composition comprising a plurality of antiretroviral compounds.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

02/07/2006 RMEBRAHT 00000121 60764811
01 FC:1005 200.00 OP

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/69033

CERTIFICATE OF COMPLIANCE

UNDER FED. R. APP. P. 32

Plaintiff-Appellant the United States of America (hereinafter "the United States" or "the Government") submits its Appellant's Brief under Rules **32(a)(5)(A),** of the Federal Rules of Appellate Procedure and **32(b)(1)** of the Federal Circuit Rules.

As required by Rule **32(b)(1),** I hereby certify that the Government's brief complies with the type-volume limitation therein provided, and that the Government's brief contains 13,899 words, including headings, footnotes, and quotations. I further certify that the Government's brief complies with the typeface and type style requirements of the Federal Rules of Appellate Procedure **32(a)(5)(A) and 32(a)(6)** by using 14-point proportional spacing in a Times New Roman font. The word processing program used for this brief is Microsoft Office 365 for Enterprise.

Respectfully submitted,

Dated: December 12, 2024

By: */s/* Walter W. Brown

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CERTIFICATE OF SERVICE

I hereby certify that, on this 12 December 2024, I filed the foregoing Non-Confidential Briefs for Plaintiff-Appellant, The United States, with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system. Plaintiff-Appellant's Briefs were also served via electronic email on December 12, 2024 on Counsel for Defendants-Appellees as follows:

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