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[54] METHODS OF TREATING VIRAL INFECTIONS 治療病毒感染的方法

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(54) **METHODS OF TREATING VIRAL INFECTIONS**

VERFAHREN ZUR BEHANDLUNG VON VIRUSINFEKTIONEN

MÉTHODES DE TRAITEMENT D'INFECTIONS VIRALES

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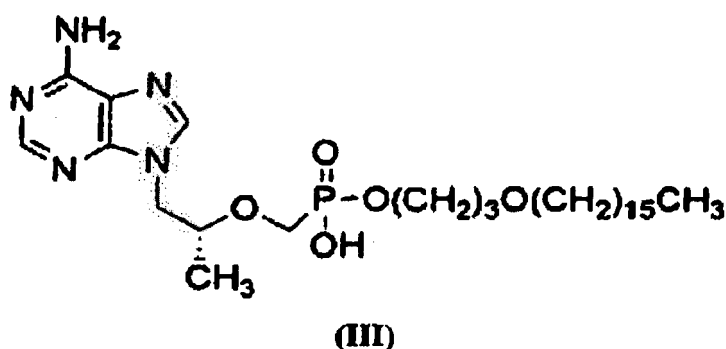
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**Description****Background of the Invention**

**[0001]** Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Combination therapy with protease inhibitors and reverse transcriptase inhibitors has a long record of effectively treating HIV and integrase inhibitors are starting to make significant contributions (See Palella, et al, N. Engl. J. Med., 338, 853-860 (1998); Richman, Nature, 410, 995-1001(2001)). However, therapy frequently fails due to the development of drug resistance, non-compliance with complicated dosing regimens, pharmacokinetic interactions, toxicity, and/or lack of potency. Therefore, there is a continuing need for new therapies that are active against mutant HIV strains, have fewer side effects, and permit simpler dosing schedules.

**Summary of the Invention**

**[0002]** In accordance with the invention there is provided an antiviral compound of Formula III:



in combination with at least one additional antiviral active agent selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc, for use in a method of treating a subject for human immunodeficiency virus (HIV) infection, wherein the subject has not been previously administered an antiviral active agent for said HIV, the method comprising administering to said subject an amount of the compound, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, effective to treat the HIV infection and inhibit the development of resistance to said compound in the subject.

**[0003]** The subject may be further infected with HBV, and said antiviral compound and at least one additional antiviral active agent is administered in an amount effective to treat both said HBV and HIV.

**[0004]** Preferably, there is provided an antiviral compound of Formula III in combination with at least one additional antiviral active agent selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc, for use in a method of treating a subject for human immunodeficiency virus (HIV) infection, wherein said subject has developed resistance or a toxic response to at least one other antiviral compound in response to prior administration of said at least one other antiviral compound to said subject for said HIV infection, the method comprising administering to said subject an amount of the compound of Formula III, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, effective to treat the HIV infection and inhibit the development of resistance to said compound in said subject.

**[0005]** The subject may be further infected with HBV, and said antiviral compound is administered in an amount effective to treat both said HBV and HIV.

**[0006]** In accordance with the invention there is also provided a pharmaceutical composition consisting of:

- (a) a first antiviral compound of Formula III as defined in claim 1, or a pharmaceutically acceptable salt, or a stereoisomer, a diastereomer, an enantiomer or racemate thereof;
- (b) one or more additional antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc; and
- (c) a pharmaceutically acceptable carrier.

**[0007]** Preferably,

- (i) the composition is in unit dose form; and/or
- (ii) the composition is in oral administration form.

**[0008]** There is herein provided an antiviral compound of Formula III, and one or more antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc, for use in a method for inhibiting sexual transmission of HIV, the method comprising topically applying to the skin or epithelial tissue of a human a therapeutically effective amount of a composition comprising the compound, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof.

Conveniently,

**[0009]**

- (i) the composition is applied intravaginally, intrarectally or to the external male genitalia; and/or
- (ii) the composition is in the form of a cream, lotion, gel, or foam; or in the form of an intra-vaginal pill, an intra-rectal pill, or a suppository; and/or
- (iii) the composition can be topically applied by release from an intravaginal device selected from a vaginal ring, a vaginal sponge, a diaphragm, or a cervical cap; or wherein the composition is topically applied from the exterior surface of a condom or vaginal applicator; and/or
- (iv) the composition further comprises a viracide effective against viral infections other than HIV; a spermicide; and/or a combination thereof; and/or
- (v) the composition further comprises a lubricant.

**[0010]** Also provided in accordance with the invention is a topical composition in the form of a cream, lotion, gel, or foam, comprising an antiviral compound of Formula III, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, wherein

- (i) the composition further comprises one or more additional anti-HIV agents; or
- (ii) the composition further comprises a viracide effective against viral infections other than HIV; or
- (iii) the composition further comprises a spermicide; or
- (iv) the composition further comprises a lubricant; or
- (v) the composition further comprises one or more additional antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc.

**[0011]** Also provided in accordance with the invention is a device for inhibiting the sexual transmission of HIV comprising: a) a barrier structure for insertion into the vaginal cavity, and b) a composition comprising an antiviral compound of Formula III as defined in claim 1, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, and one or more additional antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc.

**[0012]** Preferably,

- (i) the barrier structure is a vaginal sponge, diaphragm, cervical cap, or condom; and/or
- (ii) the device further comprises additional anti-HIV agents, a viracide effective against viral infections other than HIV, and/or a spermicide.

**[0013]** Also described herein is the finding that active compounds described herein associate or bind directly to viruses such as HIV, making possible the delivery of the active compounds into cellular or tissue compartments (sometimes referred to as "privileged compartments") to which active compounds are not otherwise accessible, and making the active compounds useful as microbicides to inhibit the transmission (e.g., prophylactically) of viruses such as HIV.

#### **Brief Description of the Drawing**

**[0014]**

**Figure 1** shows for comparative purposes the virologic response to tenofovir in antiretroviral experienced patients at 24 weeks.

**Figure 2** shows the *in vitro* efficacy of tenofovir (TFV) as compared to HDP-TFV (CMX157).

**Figure 3** shows the *in vitro* efficacy of TFV as compared to HDP-TFV (CMX157), this time with the IC<sub>50</sub>s for HDP-TFV multiplied by 100 for scaling.

### Detailed Description

**[0015]** The foregoing and other aspects of the present invention will now be described in more detail with respect to the description and methodologies provided herein. It should be appreciated that the invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

**[0016]** As used in the description and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Also, as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items. Furthermore, the term "about," as used herein when referring to a measurable value such as an amount of a compound, dose, time, temperature, and the like, is meant to encompass variations of 20%, 10%, 5%, 1%, 0.5%, or even 0.1% of the specified amount. It will be further understood that the terms "comprises" and/or "comprising," when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. Unless otherwise defined, all terms, including technical and scientific terms used in the description, have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

**[0017]** In case of a conflict in terminology, the present specification is controlling.

**[0018]** As used herein, "alkyl" refers to a straight or branched chain hydrocarbon containing from 1 to 30 carbon atoms. In some embodiments, the alkyl group contains 2 to 25, 2 to 24, 1 to 10, or 1 to 8 carbon atoms. In some embodiments the alkyl group contains 1 to 6 carbon atoms. In some embodiments, the alkyl group contains 1 to 4 carbon atoms. In still other embodiments, alkyl group contains 1-5 carbon atoms, and in yet other embodiments, alkyl group contain 1-4 or 1-3 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples which are described herein.

**[0019]** As used herein, "alkenyl," refers to a straight or branched chain hydrocarbon containing from 2 to 30 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. In some embodiments, the alkenyl group contains 2 to 25, 2 to 24, 2 to 10, 2 to 8 carbon atoms. In some embodiments, the alkenyl group contains 2 to 6 carbon atoms. In still other embodiments, alkenyl groups contain 2-5 carbon atoms, and in yet other embodiments alkenyl groups contain 2-4 or 2-3 carbon atoms. Representative examples of "alkenyl" include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl and the like. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples which are described herein.

**[0020]** As used herein, "alkynyl," refers to a straight or branched chain hydrocarbon group containing from 2 to 30 carbon atoms and containing at least one carbon-carbon triple bond. In some embodiments, the alkynyl group contains 2 to 25, 2 to 24, 2 to 10 or 2 to 8 carbon atoms. In some embodiments, the alkynyl group contains 2 to 6 carbon atoms. In still other embodiments, alkynyl groups contain 2-5 carbon atoms, and in yet other embodiments, alkynyl groups contain 2-4 or 2-3 carbon atoms. Representative examples of alkynyl include, but are not limited, to ethynyl, 1-propynyl, 2-propynyl, 3-butyne, 2-pentyne, 1-butyne and the like. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples which are described herein.

**[0021]** As used herein, the term "alkoxy" refers to an alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. In some embodiments the alkyl group contains 1-30 carbon atoms. In other embodiment, the alkyl group contains 1-20, 1-10 or 1-5 carbon atoms. In some embodiments, the alkoxy group contains 1 to 8 carbon atoms. In some embodiments, the alkoxy group contains 1 to 6 carbon atoms. In some embodiments, the alkoxy group contains 1 to 4 carbon atoms. In still other embodiments, alkoxy group contains 1-5 carbon atoms, and in yet other embodiments, alkoxy group contain 1-4 or 1-3 carbon atoms. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, and n-pentoxy. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples which are described herein.

**[0022]** As used herein, "amino acid residue" refers to a compound consisting of a carbon atom which is bonded to a primary amino (-NH<sub>2</sub>) group, a carboxylic acid (-COOH) group, a side chain, and a hydrogen atom. For example, the term "amino acid" includes, but is not limited to, Glycine, Alanine, Valine, Leucine, Isoleucine, Serine, Threonine, Aspartic

acid and Glutamic acid. In Formula I or Ia, when R<sub>2</sub> is -NR'H and R' is an amino acid residue, N is attached to the carbon atom as a side chain. Additionally, as used herein, "amino acid" also includes derivatives of amino acids such as esters, and amides, and salts, as well as other derivatives, including derivatives having pharmacoproperties upon metabolism to an active form. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples which are described herein.

**[0023]** As used herein, "cycloalkyl" refers to a monovalent saturated cyclic or bicyclic hydrocarbon group of 3-12 carbons derived from a cycloalkane by the removal of a single hydrogen atom. In some embodiments, cycloalkyl contains 3 to 8 carbon atoms. In some embodiments, cycloalkyl contains 3 to 6 carbon atoms. Cycloalkyl groups may be optionally substituted with alkyl, alkoxy, halo, or hydroxy substituents. Representative examples of cycloalkyl include, but are not limited to, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

**[0024]** As used herein, "heteroalkyl," "heteroalkenyl" or "heteroalkynyl" refer to alkyl, alkenyl or alkynyl groups which contain one or more oxygen, sulfur, nitrogen, phosphorus or silicon atoms, e.g., in place of carbon atoms. In some embodiments, the heteroalkyl group contains 1-8 carbon atoms. In certain embodiments, the heteroalkenyl and heteroalkynyl groups independently contain 2-8 carbon atoms. In still other embodiments, heteroalkyl, heteroalkenyl and heteroalkynyl independently contain 2-5 carbon atoms, and in yet other embodiments, heteroalkyl, heteroalkenyl and heteroalkynyl independently contain 2-4 or 2-3 carbon atoms.

**[0025]** The terms "heterocycle" or "heterocyclyl" represent a 3-, 4-, 5-, 6-, 7- or 8-membered saturated or unsaturated ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. In some embodiments, the heterocycle contains 3, 4, 5, or 6 carbons. Representative heterocyclyl include, but not limited to, furanyl, thiophenyl, pyrrolyl, piperidinyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, isoxazolyl, isothiazolyl, and piperazinyl.

**[0026]** As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) and the term "halo" refers to the halogen radicals: fluoro (-F), chloro (-Cl), bromo (-Br), and iodo (-I).

**[0027]** As used herein, the term "haloalkyl" refers to a straight or branched chain alkyl group as defined herein containing at least one carbon atoms substituted with at least one halo group, halo being as defined herein. In some embodiments, the haloalkyl contains 1 to 30 carbon atoms. In some embodiments, the haloalkyl contains 1 to 8 or 1 to 6 carbon atoms. In other embodiments, the haloalkyl contains 1 to 4 carbon atoms. Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples which are described herein.

**[0028]** As used herein, the term "aryl" refers to a monocyclic carbocyclic ring system or a bicyclic carbocyclic fused ring system having one or more aromatic rings. Representative examples of aryl include, azulenyl, indanyl, indenyl, naphthyl, phenyl, tetrahydronaphthyl, and the like. The term "aryl" is intended to include both substituted and unsubstituted aryl unless otherwise indicated. For example, an aryl may be substituted with one or more heteroatoms (e.g., oxygen, sulfur and/or nitrogen). Additional examples or generally applicable substituents are illustrated by the specific embodiments shown in the Examples which are described herein.

**[0029]** Subjects to be treated by the methods of the disclosure are, in general, mammalian and primate subjects (e.g., human, monkey, ape, chimpanzee). Subjects may be male or female and may be of any age, including prenatal (i.e., *in utero*), neonatal, infant, juvenile, adolescent, adult, and geriatric subjects. Thus, in some cases the subjects may be pregnant female subjects. Treatment may be for any purpose, including the therapeutic treatment of previously infected subjects, as well as the prophylactic treatment of uninfected subjects (e.g., subjects identified as being at high risk for infection).

**[0030]** As used herein, "Human immunodeficiency virus" (or "HIV") as used herein is intended to include all subtypes thereof, including HIV subtypes A, B, C, D, E, F, G, and O, and HIV-2.

**[0031]** As used herein, "Hepatitis B virus" (or "HBV") as used herein is intended to include all subtypes (adw, adr, ayw, and ayr) and or genotypes (A, B, C, D, E, F, G, and H) thereof.

**[0032]** As used herein, "Multiple nucleoside resistant" or "multi-nucleoside resistant" as used herein refers to genotypic or phenotypic patterns which predict or indicate diminished efficacy for most or all nucleoside and nucleotide reverse transcriptase inhibitors. Genotypic examples include the Q151M complex, the T69SXX complex and multiple thymidine analog associated mutations. Phenotypic examples include patterns where few or no NRTIs test as "sensitive".

**[0033]** As used herein, "Toxic response" as used herein may be any deleterious toxic and/or undesired response to a treatment with an antiviral agent, including but not limited to nausea, vomiting, rash, diarrhea, nephrotoxicity, mitochondrial toxicity, etc. and combinations thereof.

**[0034]** As used herein, a "therapeutically effective amount" or "an amount effective" refers to an amount that will provide some alleviation, mitigation, and/or decrease in at least one clinical symptom in the subject. Those skilled in the art will appreciate that the therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject.

**[0035]** Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for

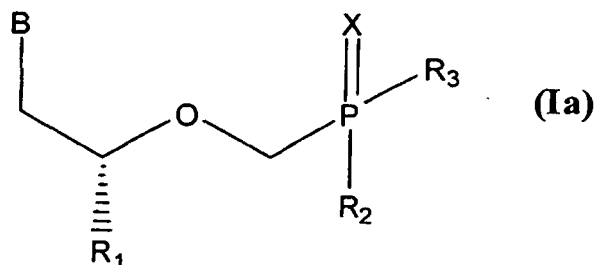
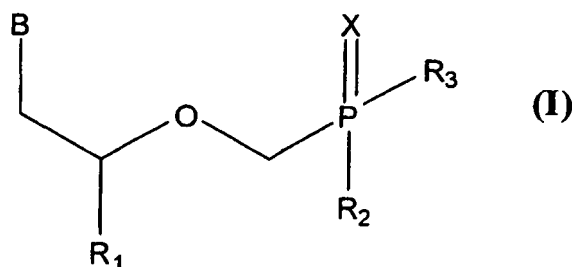
each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds and all tautomeric forms are disclosed herein.

[0036] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0037] Active compounds may optionally be administered in conjunction with other active compounds and/or agents useful in the treatment of viral infections as described herein. The other compounds may optionally be administered concurrently. As used herein, the word "concurrently" means sufficiently close in time to produce a combined effect (that is, concurrently may be simultaneously, or it may be two or more events occurring within a short time period before or after each other).

#### A. Active compounds.

[0038] Antiviral compounds of **Formula I** (and **Formula Ia**), or a pharmaceutically acceptable salt, or a stereoisomer, a diastereomer, an enantiomer or racemate thereof are described herein:



wherein:

B is a purine or pyrimidine base, including but not limited to: adenine, 6-chloropurine, xanthine, hypoxanthine, guanine, 8-bromoguanine, 8-chloroguanine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine, 2-aminopurine, 2,6-diaminopurine, thymine, cytosine, 5-fluorocytosine, uracil; 5-bromouracil, 5-iodouracil, 5-ethyluracil, 5-ethynyluracil, 5-propynyluracil, 5-propyluracil, 5-vinyluracil, 5-bromovinyluracil;

R<sub>1</sub> is H, methyl, ethyl, -CH<sub>2</sub>OH, -CH<sub>2</sub>CH<sub>2</sub>OH, -CH(OH)CH<sub>3</sub>, or C<sub>1-6</sub> haloalkyl;

R<sub>2</sub> is fluoro, hydroxy, -OR<sub>2a</sub>, -BH<sub>3</sub>, C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, C<sub>1-8</sub> heteroalkyl, C<sub>2-8</sub> heteroalkenyl, C<sub>2-8</sub> heteroalkynyl, or -NR'H;

R<sub>2a</sub> is C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, C<sub>1-8</sub> heteroalkyl, C<sub>2-8</sub> heteroalkenyl, C<sub>2-8</sub> heteroalkynyl, -P(=O)(OH)<sub>2</sub>, or -P(=O)(OH)OP(=O)(OH)<sub>2</sub>;

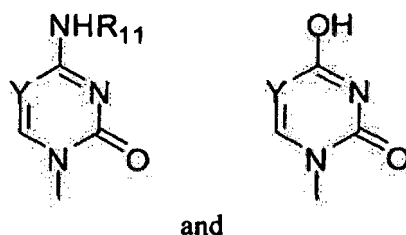
R' is C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, C<sub>1-8</sub> heteroalkyl, C<sub>2-8</sub> heteroalkynyl, C<sub>2-8</sub> heteroalkenyl, C<sub>6-10</sub> aryl, or an amino acid residue,

R<sub>3</sub> is -O(CH<sub>2</sub>)<sub>m</sub>O(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, where m is from 2 to 5 (in some embodiments, 2 or 3) and n is from 11 to 21 (in some embodiments, 15 or 17); and

X is selenium, sulphur, or oxygen (in some embodiments, oxygen)



**[0039]** Additional examples of base B include, but are not limited to, compounds of the general formula:



where:

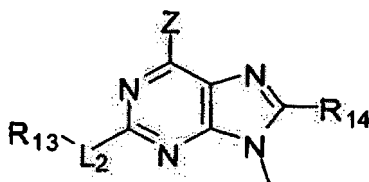
Y is N or CX;

X is selected from the group consisting of H, halo, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, CN, CF<sub>3</sub>, N<sub>3</sub>, NO<sub>2</sub>, C<sub>6-10</sub> aryl, C<sub>6-10</sub> heteroaryl, and COR<sub>b</sub>;

R<sub>b</sub> is selected from the group consisting of H, OH, SH, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> aminoalkyl, C<sub>1-6</sub> alkoxy and C<sub>1-6</sub> thioalkyl; and

R<sub>11</sub> is selected from the group consisting of H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>6-10</sub> aryl, and carbonyl substituted with a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, or C<sub>6-10</sub> aryl. The example of B is further described in U.S. Patent No. 6,583,149.

**[0040]** Additional examples of base B include, but are not limited to, compounds of the general formula:



where:

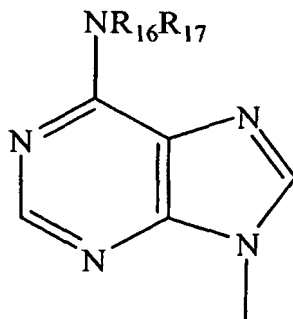
Z is NH<sub>2</sub> or hydroxyl;

L<sub>2</sub> is a covalent bond (that is, is absent), -N(-R<sub>15</sub>)-, N(-R<sub>15</sub>)C(=O)-, -O-, -S-, -S(=O)-, or is -S(=O)<sub>2</sub>-,

R<sub>13</sub> is H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> heteroalkyl, C<sub>2-6</sub> alkenyl, C<sub>6-10</sub> aryl, C<sub>7-16</sub> arylalkyl, C<sub>3-10</sub> carbocyclyl, C<sub>6-10</sub> heterocyclyl, or C<sub>7-16</sub> heterocyclylalkyl;

R<sub>14</sub> is H, halo, hydroxy, alkoxy, -O(CH<sub>2</sub>)<sub>x</sub>OC(=O)OR<sub>15</sub>, or OC(=O)OR<sub>15</sub>, wherein X is 2 or 3 to 10, 15 or 20, and R<sub>15</sub> is H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> heteroalkyl, C<sub>2-6</sub> alkenyl, C<sub>6-10</sub> aryl, C<sub>7-16</sub> arylalkyl, C<sub>3-10</sub> cyclyl, C<sub>6-10</sub> heterocyclyl, or C<sub>7-16</sub> heterocyclylalkyl.

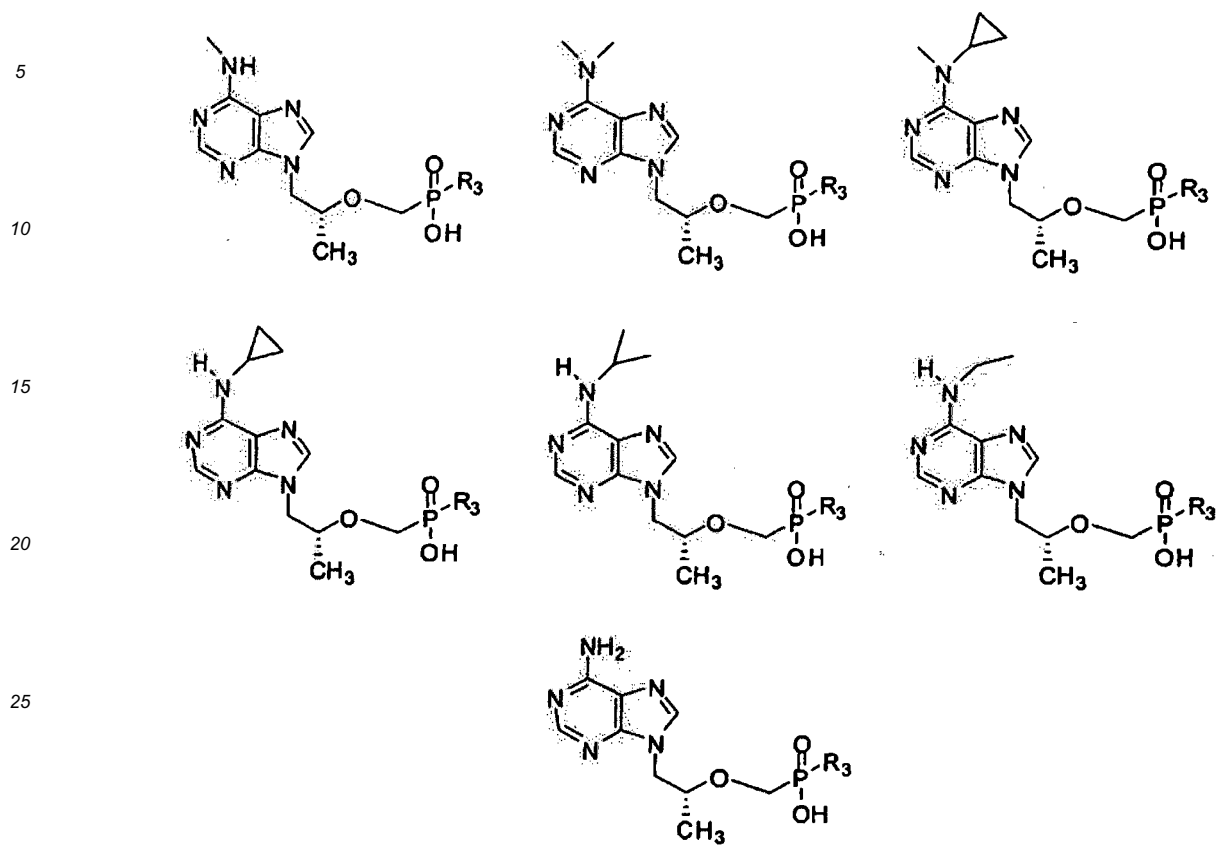
**[0041]** Additional examples of base B includes, but not limited to, compounds of the general formula:



**[0042]** R<sub>16</sub> and R<sub>17</sub> are independently selected from the group consisting of hydrogen, C<sub>1-6</sub> alkyl, or C<sub>3-6</sub> cycloalkyl, or N, R<sub>16</sub> and R<sub>17</sub> taken together to form N<sub>3</sub>, C<sub>3-8</sub> heterocyclyl, wherein C<sub>3-6</sub> cycloalkyl and C<sub>3-8</sub> heterocyclyl can be optionally substituted with one or more C<sub>1-5</sub> alkyl.

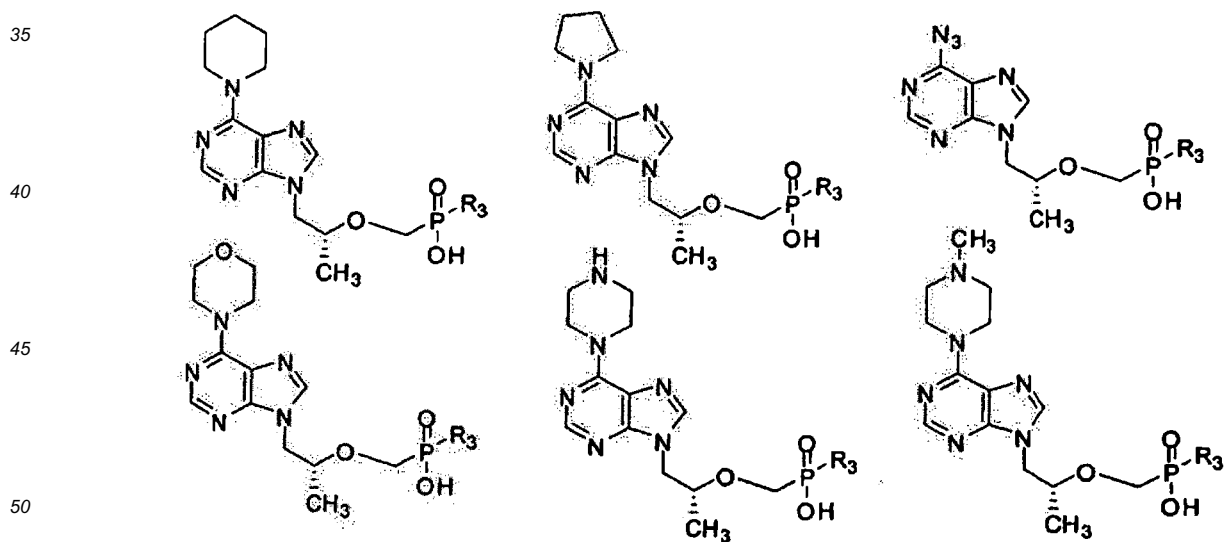
**[0043]** Exemplary active compounds (tenofovir analogs) useful for carrying out the present invention include, but are

not limited to:

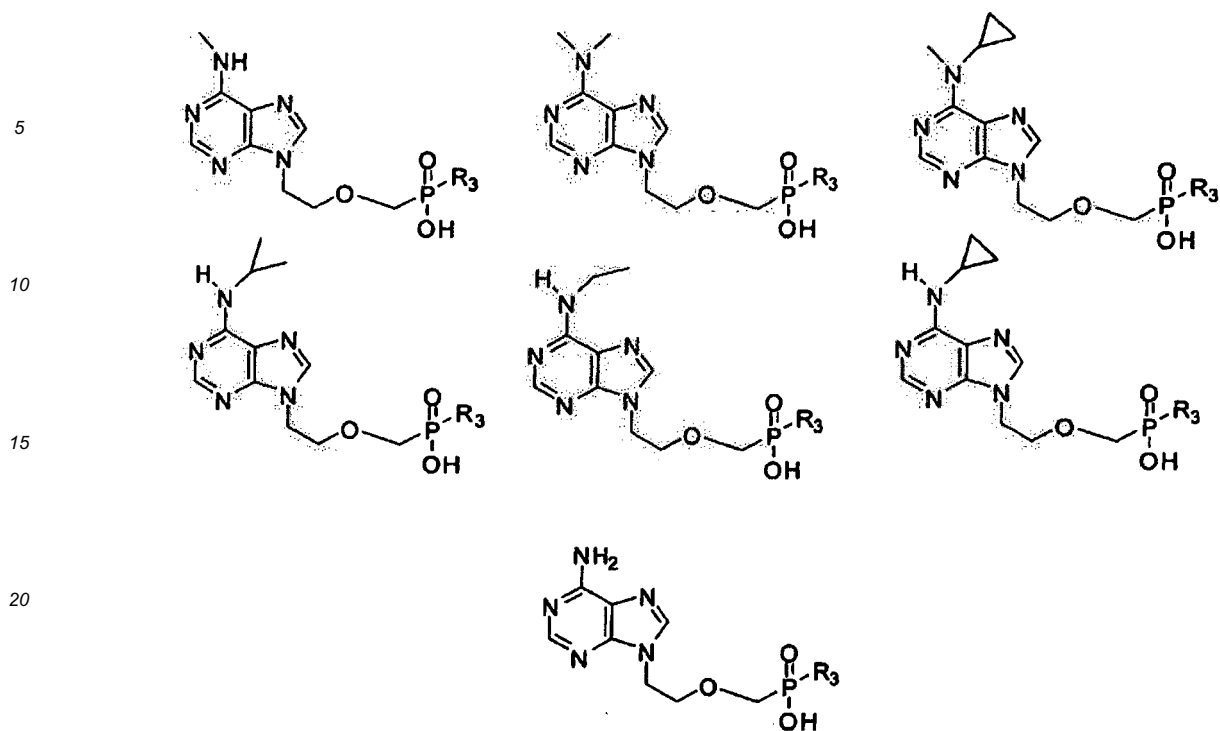


where  $R_3$  is:  $O(CH_2)_2O(CH_2)_{17}CH_3$  or  $O(CH_2)_3O(CH_2)_{15}CH_3$

**[0044]** Additional examples of active compounds (tenofovir analogs) includes:

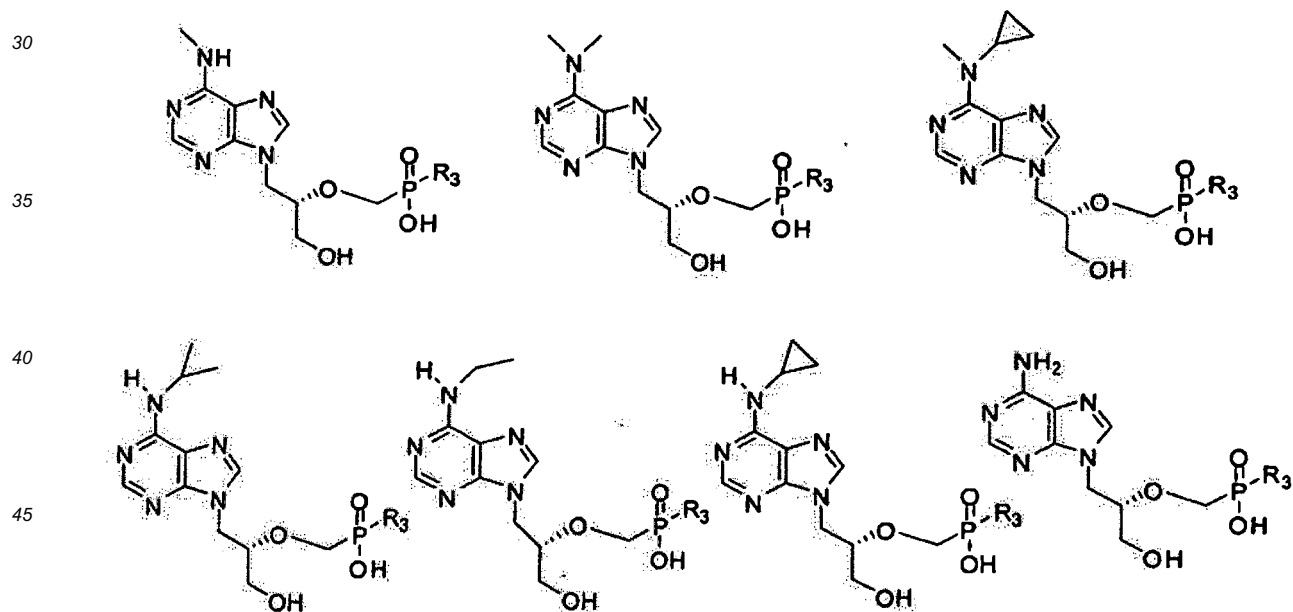


wherein  $R_3$  is  $O(CH_2)_2O(CH_2)_{17}CH_3$  or  $O(CH_2)_3O(CH_2)_{15}CH_3$  Additional examples of active compounds (adefovir analogs) include:



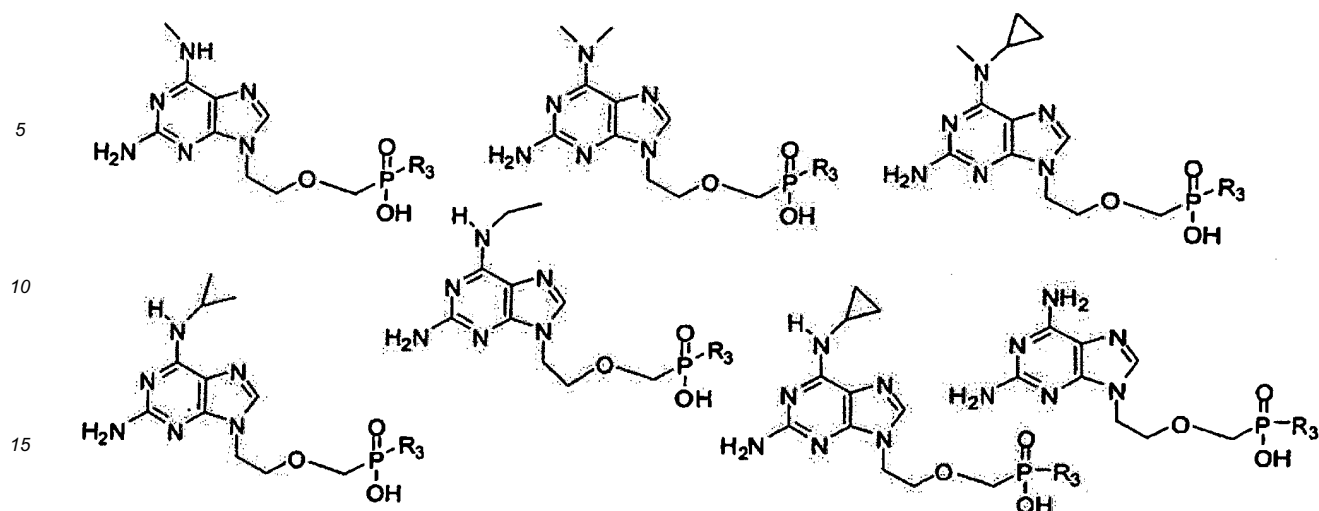
where  $R_3$  is:  $O(CH_2)_2O(CH_2)_{17}CH_3$  or  $O(CH_2)_3O(CH_2)_{15}CH_3$

**[0045]** Additional examples of active compounds (HPMPA analogs) includes:



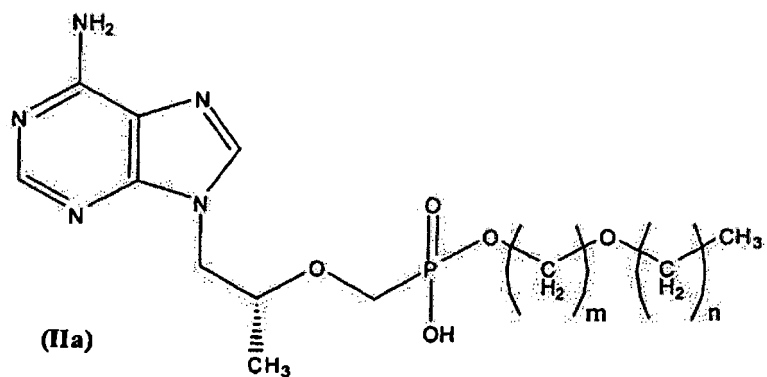
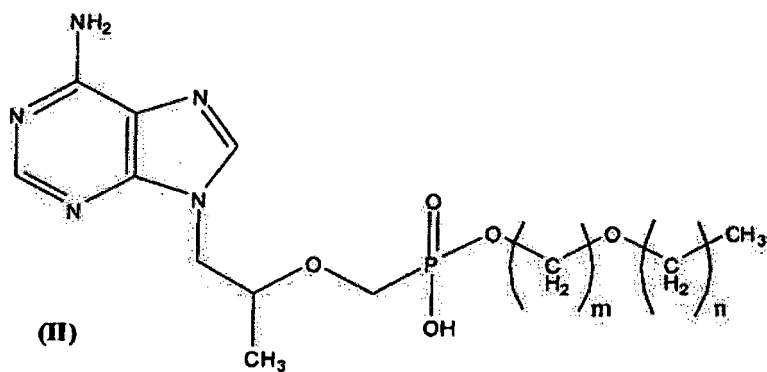
where  $R_3$  is:  $O(CH_2)_2O(CH_2)_{17}CH_3$  or  $O(CH_2)_3O(CH_2)_{15}CH_3$

**[0046]** Additional examples of active compounds (PMEG analogs) include



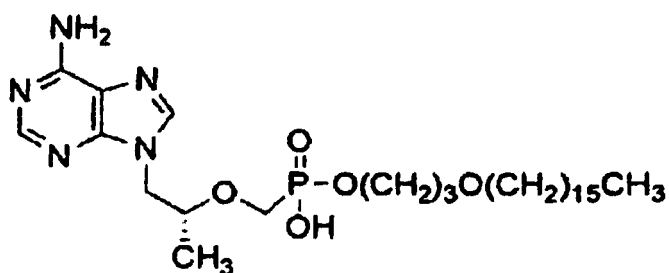
where  $R_3$  is:  $O(CH_2)_2O(CH_2)_{17}CH_3$  or  $O(CH_2)_3O(CH_2)_{15}CH_3$

[0047] Lipid tenofovir conjugates such as compounds of Formula II (and Formula IIa) are described herein:



where  $m$  is from 2 to 5 (in some embodiments, 3) and  $n$  is from 11 to 21 (in some embodiments, 15 or 17), or a pharmaceutically acceptable salt, or a stereoisomer, a diastereomer, an enantiomer or racemate thereof.

[0048] The compound for use in the invention is a compound of Formula III (also referred to as CMX157 herein):

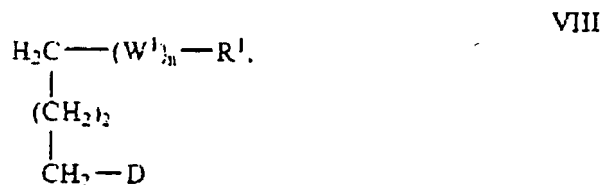
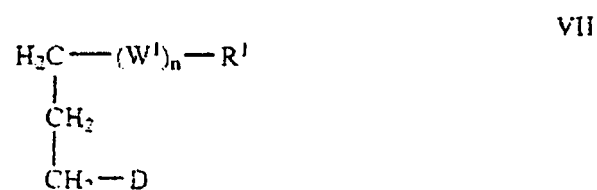
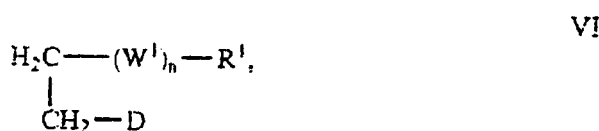
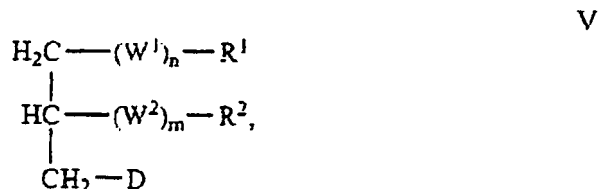


(III) CMX 157

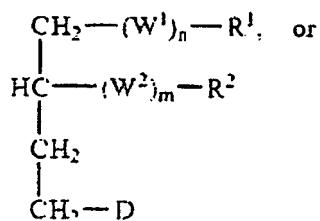
or a pharmaceutically acceptable salt, or a stereoisomer, a diastereomer, an enantiomer or racemate thereof.

**[0049]** Such compounds are known and described in, for example, G. Painter et al., Evaluation of Hexadecyloxypropyl-9-R-[2-(Phosphonomethoxy)Propyl]-Adenine, CMX157, as a Potential Treatment for Human Immunodeficiency Virus Type 1 and Hepatitis B Virus Infections, Antimicrobial Agents and Chemotherapy 51, 3505-3509 (2007); U.S. Patent Nos. 7,034,014 to Hostetler, and US Patent No. 6,716,825 to Hostetler, and/or can be prepared by modification of known techniques including but not limited to those described in PCT Patent Applications WO2005/79812 A1 (Anadys Pharmaceuticals) and WO2008/10921 A2 (Gilead).

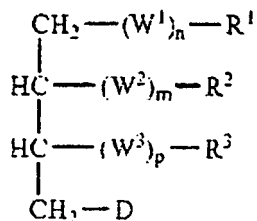
**[0050]** In addition to the compounds described in connection with **Formulas I-III** above, a variety of lipid derivatives of acyclic nucleotide phosphonates such as tenofovir can be used as active agents in the methods and compositions provided herein. In one embodiment, the active agents have the following structures:



IX



X

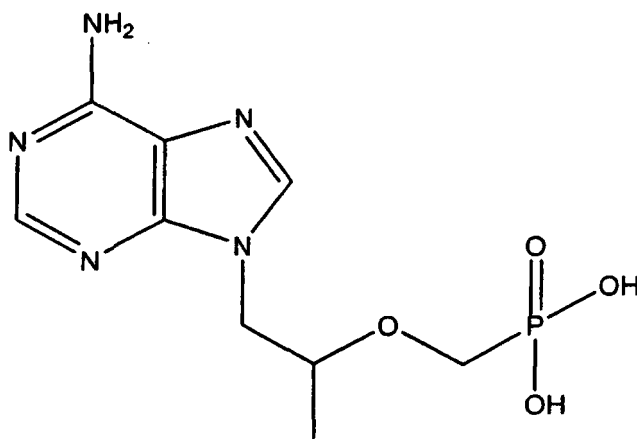


wherein  $\text{W}^1$ ,  $\text{W}^2$ , and  $\text{W}^3$  are each independently -O-, -S-, -SO-, -SO<sub>2</sub>-, -O(C=O)-, -(C=O)O-, -NH(C=O)-, -(C=O)NH- or -NH-; and in one embodiment are each independently O, S, or -O(C=O)-; n is 0 or 1; m is 0 or 1; p is 0 or 1;

$\text{R}^1$  is an optionally substituted alkyl, alkenyl or alkynyl, e.g., C<sub>1-30</sub> alkyl, C<sub>2-30</sub> alkenyl, or C<sub>2-30</sub> alkynyl; or in one embodiment,  $\text{R}^1$  is optionally substituted C<sub>8-30</sub> alkyl, C<sub>8-30</sub> alkenyl or C<sub>8-30</sub> alkynyl, or  $\text{R}^1$  is a C<sub>8-24</sub> alkyl, C<sub>8-24</sub> alkenyl or C<sub>8-24</sub> alkynyl (e.g., C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, or C<sub>24</sub> alkyl, alkenyl, or alkynyl);

$\text{R}^2$  and  $\text{R}^3$  are each independently an optionally substituted C<sub>1-25</sub> alkyl, C<sub>2-25</sub> alkenyl, or C<sub>2-25</sub> alkynyl;

D may be tenofovir directly linked to a methylene group as depicted in Formulas V-X, e.g., D is a moiety of the formula:



(e.g., Tenofovir is directly linked to the methylene group of formula V-X via the phosphonate hydroxyl group).

**[0051]** In some embodiments of Formulas V-X:

$\text{W}^1$ ,  $\text{W}^2$ , and  $\text{W}^3$  are each independently -O-, -S-, or -O(CO)-;

n is 0 or 1; m is 0 or 1; p is 0 or 1;

$\text{R}^1$  is optionally substituted C<sub>12-24</sub> alkyl or alkenyl (e.g., C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, or C<sub>24</sub> alkyl or alkenyl);

$\text{R}^2$  and  $\text{R}^3$  are each independently optionally substituted C<sub>1-24</sub> alkyl or C<sub>2-24</sub> alkenyl, or C<sub>2-24</sub> alkynyl.

D is tenofovir linked directly to a methylene group as depicted in Formulas V-X.

**[0052]** In another subembodiment, the active compound has one of the following structures: wherein  $\text{R}^1$  is an optionally substituted C<sub>8-24</sub> alkyl, for example, C<sub>12-24</sub> alkyl, D is tenofovir linked directly to a methylene group as depicted in Formulas V-X.

**[0053]** The active compounds disclosed herein can, as noted above, be provided in the form of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent

compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of lithium, sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

**[0054]** Active compounds as described herein can be prepared in accordance with known procedures, or variations thereof that will be apparent to those skilled in the art. See, e.g., Painter et al., Evaluation of Hexadecyloxypropyl-9-R-[2-(Phosphonomethoxy)Propyl]-Adenine, CMX157, as a Potential Treatment for Human Immunodeficiency Virus Type 1 and Hepatitis B Virus Infections, Amimicrobial Agents and Chemotherapy 51, 3505 3509 (2007) and US Patent Application Publication No. 2007/0003516 to Almond et al.

#### **B. Additional antiviral agents/compounds.**

**[0055]** Antiviral active agents include HIV-protease inhibitors, nucleoside reverse transcriptase inhibitors (this term herein including nucleotide reverse transcriptase inhibitors), non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors, fusion inhibitors, maturation inhibitors, and combinations thereof. Numerous examples are known and described in, for Example, US Patent Application Publication No. 2006/0234982 to Dahl et al. at **Table A** therein, and in **Table A** as set forth below.

**[0056]** Additional examples include, but are not limited to the integrase inhibitor Isentress or raltegravir (MK-0518: Merck), the CCR5 inhibitor Maraviroc or selzentry (and K-427857, Pfizer) and others of these classes.

**[0057]** Additional examples are provided in US Patent No 7,094,413 to Buelow et al.; US Patent No. 7,250,421 to Nair et al., US Patent Application Publication No. 2007/0265227 to Heneine et al and US Patent Application Publication No. 2007/0072831 to Cai et al.

**[0058]** The non-nucleoside reverse transcriptase inhibitor ("NNRTI") 6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H3,1-benzoxazin-2-one, and pharmaceutically acceptable salts thereof, are described in, for example, US Patent No. 5,519,021. For example, efavirenz.

**[0059]** The nucleoside reverse transcriptase inhibitor ("NRTI") 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1, 3-oxathiolane ("FTC") and pharmaceutically acceptable salts thereof, are described in, for example, US Patent No. 6,642,245 to Liotta et al. For example, emtricitabine.

**[0060]** Integrase inhibitors include but are not limited to those described in US Patent Application Publication No. 2007/0072831, WO 02/30426, WO 02/30930, WO 02/30931, WO 02/055079, WO 02/36734, U.S. Patent No. 6,395,743; U.S. Patent No. 6,245,806; U.S. Patent No. 6,271,402; WO 00/039086; WO 00/075122; WO 99/62513; WO 99/62520; WO 01/00578; Jing, et al., Biochemistry, 41, 5397-5403, (2002); Pais, et al., J. Med. Chem., 45, 3184-94 (2002); Goldgur, et al., Proc. Natl. Acad. Sci. U.S.A., 96, 13040-13043 (1999); Espeseth, et al., Proc. Natl. Acad. Sci. U.S.A., 97, 11244-11249, (2000); WO 2005/016927, WO 2004/096807, WO 2004/035577, WO 2004/035576 and US 2003/0055071.

TABLE A

	5,6 dihydro-5-azacytidine
	5-aza 2'-deoxycytidine
	5-azacytidine
	5-yl-carbocyclic 2'-deoxyguanosine (BMS200,475)
	9 (arabinofuranosyl)guanine; 9-(2' deoxyribofuranosyl)guanine
	9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine
	9-(2'-deoxy 2'fluororibofuranosyl)guanine
	9-(2'-deoxyribofuranosyl)-2,6 diaminopurine
	9-(arabinofuranosyl)-2,6 diaminopurine
	Abacavir, Ziagen®
	Acyclovir, ACV; 9-(2-hydroxyethoxymethyl)guanine
	Adefovir dipivoxil, Hepsera ®
	amdoxivir, DAPD
	Amprenavir, Agenerase ®

(continued)

	araA; 9-β-D-arabinofuranosyladenine (Vidarabine)
	atazanivir sulfate (Reyataz ®)
5	AZT; 3'-azido-2',3'-dideoxythymidine, Zidovudine, (Retrovir ®)
	BHCG; (.+.-)-(1a,2b,3a)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine
	BMS200,475; 5-yl-carbocyclic 2'-deoxyguanosine
	Buciclovir; (R) 9-(3,4-dihydroxybutyl)guanine
10	BvaraU; 1-β-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (Sorivudine)
	Calanolide A
	Capravirine
	CDG; carbocyclic 2'-deoxyguanosine
	Cidofovir, HPMPC; (S)-9-(3-hydroxy-2-
15	phosphonylmethoxypropyl)cytosine
	Clevudine, L-FMAU; 2'-Fluoro-5-methyl-β-L-arabino-furanosyluracil
	Combivir ® (lamivudine/zidovudine)
	Cytallene; [1-(4'-hydroxy-1',2'-butadienyl)cytosine]
20	d4C; 3'-deoxy-2',3'-didehydrocytidine
	DAPD; (-)-β-D-2,6-diaminopurine dioxolane
	ddA; 2',3'-dideoxyadenosine
	ddAPR; 2,6-diaminopurine-2',3'-dideoxyriboside
	ddC; 2',3'-dideoxycytidine (Zalcitabine)
25	ddl; 2',3'-dideoxyinosine, didanosine, (Videx ®, Videx ® EC)
	Delavirdine, Rescriptor ®
	Didanosine, ddl, Videx ®; 2',3'-dideoxyinosine
	DXG; dioxolane guanosine
	E-5-(2-bromovinyl)-2'-deoxyuridine
30	Efavirenz, Sustiva ®
	Enfuvirtide, Fuzeon ®
	F-ara-A; fluoroarabinosyladenosine (Fludarabine)
	FDOC; (-)-β-D-5-fluoro-1-[2-(hydroxymethyl)-1,3-dioxolane]cytosine
35	FEAU; 2'-deoxy-2'-fluoro-1-β-D-arabinofuranosyl-5-ethyluracil
	FIAC; 1-(2-deoxy-2-fluoro-β-D-arabinofurao syl)-5-iodocytosine
	FIAU; 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouridine
	FLG; 2',3'-dideoxy-3'-fluoroguanosine
	FLT; 3'-deoxy-3'-fluorothymidine
40	Fludarabine; F-ara-A; fluoroarabinosyladenosine
	FMAU; 2'-Fluoro-5-methyl-β-L-arabino-furanosyluracil
	FMdC
	Foscarnet; phosphonoformic acid, PFA
45	FPMPA; 9-(3-fluoro-2-phosphonylinethoxyppm)adenine
	Gancyclovir, GCV; 9-(1,3-dihydroxy-2-propoxymethyl)guanine
	GS-7340; 9-[R-2-[[[(S)-1-(isopropoxycarbonyl)ethyl]amino]-
	phenoxyphosphinypl methoxy]propyl]adenine
	HPMPA; (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine
50	HPMPC; (S)-9-(3-hydroxy-2-phosphonylinethoxypropyl)cytosine
	(Cidofovir)
	Hydroxyurea, Droxia ®
	Indinavir, Crixivan ®
55	Kaletra ® (lopinavir/ritonavir)
	Lamivudine, 3TC, Epivir™; (2R, 5S, cis)-4-amino-1-(2-
	hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one
	L-d4C; L-3'-deoxy-2',3'-didehydrocytidine



(continued)

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L-ddC; L-2',3'-dideoxycytidine  
 L-Fd4C; L-3'-deoxy-2',3'-didehydro-5-fluorocytidine  
 L-FddC; L-2',3'-dideoxy-5-fluorocytidine  
 Lopinavir  
 Nelfinavir, Viracept ®  
 Nevirapine, Viramune ®  
 Oxetanocin A; 9-(2-deoxy-2-hydroxymethyl-β-D-erythro-  
 oxetanosyl)adenine  
 Oxetanocin G; 9-(2-deoxy-2-hydroxymethyl-β-D-erythro-  
 oxetanosyl)guanine  
 Penciclovir  
 PMEDAP; 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine  
 PMPA, tenofovir; (R)-9-(2-phosphonylmethoxypropyl)adenine  
 PPA; phosphonoacetic acid  
 Ribavirin; 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide  
 Ritonavir, Norvir ®  
 Saquinavir, Invirase ®, Fortovase ®  
 Sorivudine, BvaraU; 1-β-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil  
 Stavudine, d4T, Zerit ®; 2',3'-didehydro-3'-deoxythymidine  
 Trifluorothymidine, TFT; Trifluorothymidine  
 Trizivir ® (abacavir sulfate/lamivudine/zidovudine)  
 Vidarabine, araA; 9-β-D-arabinofuranosyladenine  
 Viread ®, tenofovir disoproxil fumarate (DF), Bis POC PMPA, TDF;  
 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[[(1R)-2-  
 (6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl)  
 ester, 5-oxide, (2E)-2-butenedioate (1:1)  
 Zalcitabine, Hivid ®, ddC; 2',3'-dideoxycytidine  
 Zidovudine, AZT, Retrovir ®; 3'-azido-2',3'-dideoxythymidine  
 Zonavir; 5-propynyl-1-ambinosyluracil

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### **C. Pharmaceutical formulations and administration.**

**[0061]** Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions include but are not limited to those described in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co. (1990) (See also US Patent Application US 2007/0072831).

**[0062]** The compounds of the invention and those herein described may be formulated with conventional carriers, diluents and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders, diluents and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

**[0063]** Compounds and their physiologically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

**[0064]** While it is possible for the active ingredients to be administered alone it is preferably to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, comprise at least one active ingredient, as above defined, together with one or more pharmaceutically acceptable carriers (excipients, diluents, etc.) thereof and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

**[0065]** The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal

or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

**[0066]** Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

**[0067]** A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

**[0068]** For infections of the eye or other external tissues e.g. mouth and skin, the formulations are, in some embodiments, applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), in some embodiments, 0.2 to 15% w/w and in other embodiments, 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

**[0069]** If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

**[0070]** The oily phase of the emulsions may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. In some embodiments, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. In some embodiments, it includes both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

**[0071]** Emulgents and emulsion stabilizers suitable for use in the formulation herein described include Tween.TM.60, Span. TM.80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

**[0072]** The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. In some embodiments, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

**[0073]** Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. In some embodiments, the active ingredient is present in such formulations in a concentration of 0.5 to 20%. In some embodiments, the active ingredient is present in a concentration of 0.5 to 10%. In some embodiments, the active ingredient is present in a concentration of about 1.5% w/w.

**[0074]** Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

**[0075]** Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

**[0076]** Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns

in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as pentamidine for treatment of pneumocystis pneumonia.

**[0077]** Formulations suitable for vaginal administration may be presented as pessaries, rings, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

**[0078]** Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

**[0079]** It should be understood that in addition to the ingredients particularly mentioned above the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

**[0080]** The present disclosure further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

**[0081]** Compounds of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods. Controlled release formulations may be employed for the treatment or prophylaxis of various microbial infections particularly human bacterial, human parasitic protozoan or human viral infections caused by microbial species including Plasmodium, Pneumocystis, herpes viruses (CMV, HSV 1, HSV 2, VZV, and the like), retroviruses, adenoviruses and the like. The controlled release formulations can be used to treat HIV infections and related conditions such as tuberculosis, malaria, pneumocystis pneumonia, CMV retinitis, AIDS, AIDS-related complex (ARC) and progressive generalized lymphadenopathy (PGL), and AIDS-related neurological conditions such as multiple sclerosis, and tropical spastic paraparesis. Other human retroviral infections that may be treated with the controlled release formulations include Human T-cell Lymphotropic virus and HIV-2 infections.

**[0082] *Pharmacokinetic enhancers.*** The compounds of the invention may be employed in combination with pharmacokinetic enhancers (sometimes also referred to as "booster agents").

**[0083]** An effective amount of an enhancer enhances or "boosts" the pharmacokinetics of a compound. An effective amount of an enhancer, for example, the amount required to enhance an active compound or additional active compound is the amount necessary to improve the pharmacokinetic profile or activity of the compound when compared to its profile when used alone. The compound possesses a better efficacious pharmacokinetic profile than it would without the addition of the enhancer. The amount of pharmacokinetic enhancer used to enhance the potency of the compound is, preferably, subtherapeutic (e.g., dosages below the amount of booster agent conventionally used for therapeutically treating infection in a patient). An enhancing dose for the compounds is subtherapeutic for treating infection, yet high enough to effect modulation of the metabolism of the compounds, such that their exposure in a patient is boosted by increased bioavailability, increased blood levels, increased half life, increased time to peak plasma concentration, increased/faster inhibition of HIV integrase, RT or protease and/or reduced systematic clearance. One example of a pharmacokinetic enhancer is RITONAVIR™ (Abbott Laboratories).

**[0084] *Combinations.*** The compositions disclosed herein can include the active compounds as described in section A above in combination with one or more (e.g., 1, 2, 3) additional active agents such as described in section B above, in analogous manner as known in the art. For example, combinations of efavirenz (an NRTI), emtricitabine (an NNRTI) and tenofovir DF (an NRTI) are described in, for example, Dahl et al., US Patent Application Publication No. 2007/0099902 to Dahl et al. Specific examples of such combinations include, but are not limited to: CMX157 or a pharmaceutically acceptable salt) in combination with:

- (a) FTC/Efavirenz;
- (b) 3TC/Efavirenz;
- (c) AZT/3TC;
- (d) FTC;
- (e) 3TC;
- (f) FTC/Isentress;
- (g) 3TC/Isentress;
- (h) PPL-100;
- (i) FTC/TMC278;
- (k) 3TC/TMC278;
- (l) FTC/TMC125; or
- (m) 3TC/TMC125.

#### **D. Treatment of privileged compartment infections.**

**[0085]** As noted above, it has also been found that active agents disclosed herein surprisingly associate or bind to viral particles. Since viral particles migrate or permeate into cellular or tissue compartments that are not generally accessible to active therapeutic agents (thus creating a substantially untreated "reservoir" of infection when subjects are systemically administered such agents), this finding makes possible (a) the treatment of infection in such privileged compartments, and (b) the use of active agents in prophylactic or microbicidal treatments (where association or binding of the active agent to virus before infection occurs is of therapeutic benefit).

**[0086]** In general, a privileged compartment is a cellular or tissue compartment to which said virus permeates in vivo, to which said active agent does not efficiently permeate in vivo in the absence of said virus, and to which said active agent is carried in vivo by said virus when said active agent binds to said virus. For example, when the privileged compartment is a tissue compartment, it may be brain (central nervous system), lymphoid, or testes. Examples of cellular privileged compartments include but are not limited to dendritic cells, microglia, monocyte/macrophages, and combinations thereof. Compositions and methods of treating privileged compartment infections may be prepared and carried out as described above. Prophylactic compositions, devices and methods are discussed in further detail below.

#### **E. Topical compositions and microbicidal methods.**

**[0087]** Topical compositions containing the active agents described herein for inhibiting or combating viral infections, e.g., for prophylactic use are described herein. Such compositions (with active agents other than those disclosed herein) are known and described in, for example, US Patent No. 6,545,007.

**[0088]** Such compositions can take several forms. Thus, in one embodiment the composition is in the form of a cream, lotion, gel, or foam that is applied to the affected skin or epithelial cavity, and preferably spread over the entire skin or epithelial surface which is at risk of contact with bodily fluids. Such formulations, which are suitable for vaginal or rectal administration, may be present as aqueous or oily suspensions, solutions or emulsions (liquid formulations) containing in addition to the active ingredient, such carriers as are known in the art to be appropriate. For "stand-alone" lubricants (i.e., lubricants that are not pre-packaged with condoms), gels and similar aqueous formulations are generally preferred, for various reasons (both scientific and economic) known to those skilled in the art. These formulations are useful to protect not only against sexual transmission of HIV, but also to prevent infection of a baby during passage through the birth canal. Thus the vaginal administration can take place prior to sexual intercourse, during sexual intercourse, and immediately prior to childbirth.

**[0089]** One method of applying an antiviral lubricant to the genitals, for the purposes disclosed herein, involves removing a small quantity (such as a teaspoon, or several milliliters) of a gel, cream, ointment, emulsion, or similar formulation from a plastic or metallic tube, jar, or similar container, or from a sealed plastic, metallic or other packet containing a single dose of such composition, and spreading the composition across the surface of the penis immediately before intercourse. Alternate methods of emplacement include: (1) spreading the composition upon accessible surfaces inside the vagina or rectum shortly before intercourse; and (2) emplacing a condom, diaphragm, or similar device, which has already been coated or otherwise contacted with an anti-viral lubricant, upon the penis or inside the vagina. In a preferred embodiment, any of these methods of spreading an anti-viral lubricant across the surfaces of the genitals causes the lubricant to coat and remain in contact with the genital and epithelial surfaces throughout intercourse.

**[0090]** In one embodiment the compositions are used in conjunction with condoms, to enhance the risk-reducing effectiveness of condoms and provide maximum protection for users. The composition can either be coated onto condoms during manufacture, and enclosed within conventional watertight plastic or foil packages that contain one condom per package, or it can be manually applied by a user to either the inside or the outside of a condom, immediately before use.

**[0091]** As used herein, "condom" refers to a barrier device which is used to provide a watertight physical barrier

between male and female genitalia during sexual intercourse, and which is removed after intercourse. This term includes conventional condoms that cover the penis; it also includes so-called "female condoms" which are inserted into the vaginal cavity prior to intercourse. The term "condom" does not include diaphragms, cervical caps or other barrier devices that cover only a portion of the epithelial membranes inside the vaginal cavity. Preferably, condoms should be made of latex or a synthetic plastic material such as polyurethane, since these provide a high degree of protection against viruses.

[0092] In another embodiment the composition is in the form of an intra-vaginal pill, an intra-rectal pill, or a suppository. The suppository or pill should be inserted into the vaginal or rectal cavity in a manner that permits the suppository or pill, as it dissolves or erodes, to coat the vaginal or rectal walls with a prophylactic layer of the anti-HIV agent.

[0093] In still another embodiment the composition is topically applied by release from an intravaginal device. Devices such as vaginal rings, vaginal sponges, diaphragms, cervical caps, female condoms, and the like can be readily adapted to release the composition into the vaginal cavity after insertion.

[0094] Compositions used in the methods of this disclosure may also comprise additional active agents, such as another agent(s) to prevent HIV infection, and agents that protect individuals from conception and other sexually transmitted diseases. Thus, in another embodiment, the compositions used further comprise one or more additional anti-HIV agents, virucides effective against viral infections other than HIV, and/or spermicides.

[0095] In one particular embodiment, the composition contains nonoxynol, a widely-used spermicidal surfactant. The resulting composition could be regarded as a "bi-functional" composition, since it would have two active agents that provide two different desired functions, in a relatively inert carrier liquid; the nonoxynol would provide a spermicidal contraceptive agent, and the DABO would provide anti-viral properties. The nonoxynol is likely to cause some level of irritation, in at least some users; this is a regrettable but is a well-known side effect of spermicidal surfactants such as nonoxynol and octoxynol, which attack and destroy the lipid bilayer membranes that surround sperm cells and other mammalian cells.

[0096] The compositions may also contain a lubricant that facilitates application of the composition to the desired areas of skin and epithelial tissue, and reduces friction during sexual intercourse. In the case of a pill or suppository, the lubricant can be applied to the exterior of the dosage form to facilitate insertion.

[0097] In still another embodiment there is provided a device for inhibiting the sexual transmission of HIV comprising (a) a barrier structure for insertion into the vaginal cavity, and (b) a composition comprising an active agent as described herein. As mentioned above, preferred devices which act as barrier structures, and which can be adapted to apply anti-HIV agent, include the vaginal sponge, diaphragm, cervical cap, or condom (male or female).

[0098] The methods, compositions and devices described herein can be adapted generally to release active agent in a time sensitive manner that best corresponds to the timing of sexual activity. When topically applied as a lotion or gel, the compositions are preferably applied immediately prior to sexual activity. Other modes of application, such as devices and suppositories, can be designed to release active agent over a prolonged period of time, at a predetermined rate, depending upon the needs of the consumer.

[0099] The present invention and the present disclosure will now be described in more detail with reference to the following examples. However, these examples are given for the purpose of illustration and are not to be construed as limiting the scope of the invention

## EXAMPLE 1

### [0100]

**Figure 1** demonstrates, for comparative purposes, the virologic response to tenofovir in antiretroviral experienced patients at 24 weeks. Data is from M. Miller et al. J Infect Dis. 189: 837 (2004). The viral load response in monotherapy with TDF in naïve patients is -1.5log (Louie et al, Determining the antiviral activity of tenofovir disoproxil fumarate in treatment-naïve chronically HIV-1-infected individuals, AIDS, 17, 1151 (2003)).

**Figures 2-3** show the *in vitro* efficacy of tenofovir (TFV) as compared to HDP-TFV (CMX157) in a PHENOSENSE™ HIV assay (service available from Monogram Biosciences, Inc., 345 Oyster Point Blvd., South San Francisco, CA 94080-1913 USA.) In **Figure 3**, the IC<sub>50</sub>s for CMX157 are multiplied by 100 for scaling. Results are also shown in **Table 1** below (where ABC is abacavir FTC is emtricitabine, ddI is didanosine, 3TC is lamivudine, d4T is stavudine, TFV is tenofovir and ZDV is zidovudine).

TABLE 1: ASSAY RESULTS (IC50 shown in  $\mu\text{M}$ )

PATIENT ID	NOTES	Results	ABC	CMX157	ddl	FTC	3TC	d4T	TFV	ZDV
PANEL 1	WT	IC50 Fold Change	0.86	0.93	1.01	0.78	0.86	0.86	0.79	0.72
		IC50	1.520000	0.001720	5.540000	0.890000	3.240000	0.510000	0.613000	0.020000
PANEL 2	WT	IC50 Fold Change	0.94	0.87	1.01	1.38	1.18	0.81	0.85	0.61
		IC50	1.670000	0.001610	5.570000	1.570000	4.440000	0.480000	0.652000	0.017000
PANEL 3	6 TAMs, no 184	IC50 Fold Change	4.43	4.58	1.59	5.02	3.70	3.66	3.47	350.00
		IC50	7.870000	0.008500	8.760000	5.730000	13.930000	2.170000	2.674000	9.562000
PANEL 6	6 TAMs + 184	IC50 Fold Change	7.91	2.81	2.06	>87.6048	>79.7162	2.28	2.16	59.00
		IC50	14.040000	0.005210	11.350000	>100	>300	1.350000	1.666000	1.610000
PANEL 7	184V	IC50 Fold Change	2.69	0.73	1.38	>87.6048	>79.7162	0.77	0.69	0.63
		IC50	4.780000	0.001360	7.570000	>100	>300	0.460000	0.534000	0.017000
PANEL 9	69ins, no 184	IC50 Fold Change	18.00	31.00	4.04	26.0C	12.00	11.00	22.0C	>915.7073
		IC50	32.650000	0.057430	22.210000	29.600000	45.880000	6.390000	16.959000	>25
PANEL 12	69ins + 184	IC50 Fold Change	26.00	6.06	4.43	>87.6048	>79.7162	11.00	4.72	319.00
		IC50	46.540000	0.011230	24.330000	>100	>300	6.790000	3.641000	8.711000

(continued)

PATIENT ID	NOTES	Results	ABC	CMX157	ddl	FTC	3TC	d4T	TFV	ZDV
PANEL 14	65R, no 184	IC50 Fold Change	3.20	1.94	1.67	17.00	19.00	1.30	1.71	0.44
		IC50	5.690000	0.003600	9.170000	19.330000	70.840000	0.770000	1.319000	0.012000
PANEL 15	65R + 184V	IC50 Fold Change	6.64	1.46	2.61	>87.6048	>79.7162	0.99	1.22	0.41
		IC50	11.780000	0.002710	14.330000	>10C	>300	0.590000	0.940000	0.01100C
PANEL 17	L74V	IC50 Fold Change	1.89	0.66	1.63	1.87	1.85	1.01	0.62	0.41
		IC50	3.360000	0.001230	8.940000	2.140000	6.980000	0.600000	0.476000	0.011000
PANEL 19	L74V + M184V	IC50 Fold Change	5.21	0.36	2.01	>87.6048	>79.7162	0.71	0.29	0.22
		IC50	9.240000	0.000660	11.060000	>100	>300	0.420000	0.227000	0.006000
PANEL 26	151M, no 184	IC50 Fold Change	19.00	1.99	12.00	30.00	24.00	9.33	2.26	93.00
		IC50	34.310000	0.003680	63.250000	34.730000	89.620000	5.540000	1.739000	2.545000
PANEL 28	151M + 184	IC50 Fold Change	>29,2959	1.64	11.00	>87.6048	>79.7162	7.10	1.43	153.00
		IC50	>52	0.003050	58.040000	>100	>300	4.220000	1.102000	4.17900C
PANEL 29	L74V -SDM	IC50 Fold Change	1.85	0.80	1.48	1.47	1.62	1.07	0.69	0.50
		IC50	3.290000	0.001480	8.14000C	1.680000	6.100000	0.630000	0.535000	0.014000

(continued)

PATIENT ID	NOTES	Results	ABC	CMX157	ddl	FTC	3TC	d4T	TFV	ZDV
PANEL 30	M184V - SDM	IC50 Fold Change	2.64	0.62	1.23	>87.6048	>79.7162	0.68	0.54	0.34
		IC50	4.680000	0.001150	6.760000C	>10C	>300	0.400000	0.413000	0.009000
PANEL	K65R - SDM	IC50 Fold Change	2.57	2.55	2.00	11.00	12.00	1.40	2.01	0.51
		IC50	4.560000	0.004730	11.020000C	12.900000C	43.330000	0.830000	1.551000	0.014000
PANEL 33	T215Y	IC50 Fold Change	2.06	2.7C	1.14	2.31	1.63	1.40	2.39	38.00
		IC50	3.670000	0.005000	6.290000	2.640000C,	6.120000	0.830000	1.843000	1.049000
PANEL 34	T215Y + M184V	IC50 Fold Change	4.29	0.90	1.43	>87.6048	>79.7162	1.10	0.81	2.61
		IC50	7.610000	0.001670	7.880000	>100	>300	0.650000	0.624000	0.071000
PANEL 35	M41 L + T215Y	IC50 Fold Change	1.89	2.11	1.14	2.74	2.01	1.41	1.84	20.00
		IC50	3.360000	0.003910	6.290000	3.130000	7.550000	0.840000	1.421000	0.557000
PANEL 37	M41L + T215Y + M184V	IC50 Fold Change	5.41	1.55	1.84	>87.6048	>79.7162	1.46	1.34	6.48
		IC50	9.600000	0.002880	10.120000	>100	>300	0.860000	1.034000	0.177000
PANEL 38	M41 L + L210W+ T215Y	IC50 Fold Change	2.80	3.21	1.36	3.70	2.74	2.06	2.80	100.00
		IC50	4.970000	0.005960	7.500000	4.220000	10.320000	1.220000	2.155000	2.722000



(continued)

PATIENT ID	NOTES	Results	ABC	CMX157	ddl	FTC	3TC	d4T	TFV	ZDV
PANEL 39	M41L+ L210W + T215Y	IC50 Fold Change	2.36	3.54	1.07	1.89	1.57	1.84	3.01	98.00
		IC50	4.190000	0.006560	5.900000	2.160000	5.890000	1.090000	2.322000	2.677000
PANEL 40	M41 L + L210W + T215Y + M184V	IC50 Fold Change	4.60	1.02	1.49	>87.6048	>79.7162	1.48	0.97	3.18
		IC50	8.170000	0.001890	8.180000	>100	>300	0.880000	0.751000	0.087000C,
PANEL 41	M41L+ L210W + T215Y + M184V	IC50 Fold Change	5.02	1.35	1.57	>87.6048	>79.7162	1.77	1.02	3.91
		IC50	8.920000	0.002500	8.640000	>100	>300	1.050000	0.789000	0.107000
PANEL 42	D67N + K70R	IC50 Fold Change	1.40	3.03	1.19	2.87	2.14	1.31	2.56	28.00
		IC50	2.480000	0.005610	6.570000	3.280000	8.070000	0.780000	1.971000	0.770000C
PANEL 44	D67N + K70R + T215F + K219E + M184V	IC50 Fold Change	4.36	1.03	1.57	>87.6048	>79.7162	1.32	0.91	7.04
		IC50	7.730000	0.00192C	8.650000	>100	>300	0.790000	0.703000	0.192000
PANEL	L210W + T215Y	IC50 Fold Change	2.05	1.50	1.00	2.29	1.93	1.58	1.34	7.58
		IC50	3.640000	0.00279C	5.510000	2.620000	7.260000	0.940000	1.033000	0.207000
PANEL 46	D67N + K70E	IC50 Fold Change	1.36	1.15	1.41	2.97	2.87	0.94	0.96	0.21
		IC50	2.420000	0.002120	7.730000	3.390000	10.800000	0.560000	0.738000	0.006000

(continued)

PATIENT ID	NOTES	Results	ABC	CMX157	ddl	FTC	3TC	d4T	TFV	ZDV
PANEL 47	D67N + K70E + M184V	IC50 Fold Change	2.85	0.78	1.32	>87.6048	>79.7162	0.70	0.64	0.15
		IC50	5.050000	0.001450	7.250000	>100	>300	0.420000	0.495000	0.004000
PANEL 48	K70E + M184V	IC50 Fold Change	5.88	0.71	1.80	>87.6048	>79.7162	0.65	0.61	0.13
		IC50	10.440000	0.00132C	9.910000	>100	>300	0.390000	0.472000	0.004000

**[0101]** The data shown in **Tables 2 and 3 below** demonstrate that CMX157 is active against all major HIV subtypes (A-G, O and HIV-2) with  $IC_{50}$ s ranging from 0.2-7.2 nanomolar.

**Table 2. Activity of Chimerix Compound CMX157 Against HIV-1 Subtype Isolates in PBMCs**

HIV-1 Isolate	Subtype	RT Endpoint		
		$IC_{50}$ (nM)	$TC_{50}$ (nM)	TI ( $TC_{50}/IC_{50}$ )
RW/92/009	A	1.75	>1,000	>571
UG/92/029	A	5.84	>1,000	>171
UG/92/037	A	2.30	>1,000	>435
ADA	B	1.08	>1,000	>925
BR/92/014	B	1.58	>1,000	>633
96USHIPS 7	B	4.80	>1,000	>208
JR-CSF	B	0.68	>1,000	>1,480
TH/92/026	B	0.44	>1,000	>2,278
BR/92/025	C	3.43	>1,000	>291
IN/93/101	C	0.53	>1,000	>1,892
MW/93/95 9	C	4.50	>1,000	>222
UG/92/001	D	5.16	>1,000	>194
UG/92/024	D	0.30	>1,000	>3,346
UG/92/046	D	0.96	>1,000	>1,039
TH/93/073	E	2.95	>1,000	>339
CMU08	E	2.81	>1,000	>356
CMU06	E	1.03	>1,000	>970
BR/93/019	F	6.40	>1,000	>156
BR/93/020	F	0.73	>1,000	>1,362
BR/93/029	F	1.03	>1,000	>972
JV1083	G	2.32	>1,000	>431
RU 132	G	1.63	>1,000	>615
G3	G	2.68	>1,000	>373
BCF01	O	7.18	>1,000	>139
BCF02	O	2.47	>1,000	>405
BCF03	O	5.29	>1,000	>189

**Table 3. Activity of Chimerix Compound CMX157 against HIV-2 Isolates in PBMCs**

HIV-2 +Isolate	RT Endpoint		
	$IC_{50}$ (nM)	$TC_{50}$ (nM)	TI ( $TC_{50}/IC_{50}$ )
CDC310319	1.77	>1,000	>564
CDC310342	4.31	>1,000	>232
CBL-20	4.48	>1,000	>223

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**[0102]** Further, these data indicate that the  $IC_{50}$ s for CMX157 against NRTI resistant HIV ranged from 1.2 to 57 nM, a median of 359-fold more potent than tenofovir (range 295-472x).

**[0103]** Finally, the data shown in Table 4 below indicates that the no-observed-adverse-effect level in rats for CMX157 for 7 days is up to 100mg/kg/day, the highest dose tested.

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Table 4. Toxicokinetic parameters on days 1 and 7 after oral administration of CMX157 to rats

Day	Dose ( mg/kg)	CMX 157 (prodrug)					Tenofovir (metabolite)				
		C <sub>max</sub> (ng/ml)	T <sub>max</sub> (h)	AUC <sub>0-24</sub> (ng · h/ml)	AUC <sub>0-∞</sub> (ng · h/ml)	t <sub>1/2elim</sub> (h)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (h)	AUC <sub>0-24</sub> (ng · h/ml)	AUC <sub>0-∞</sub> (ng · h/ml)	t <sub>1/2elim</sub> (h)
1	10	84.85	0.5	441.7	ND	ND	55.35	2.0	510.8	775.2	10.9
7	10	110.90	0.5	435.2	ND	ND	49.55	2.4	964.7	1,226.9	9.2
1	30	379.00	2.0	1,832.8	ND	ND	109.10	4.0	1,456.1	1,808.1	10.1
7	30	202.50	1.0	1,543.9	ND	ND	149.25	4.0	2,363.4	2,790.5	7.6
1	100	905.00	2.0	5,408	5,429.8	2.5	181.40	12.0	3,039.3	3,639.5	7.2
7	100	685.50	2.0	8,046.3	8,050.6	1.6	322.00	12.0	5,715.4	7,373.4	9.0

a Plasma was obtained at 0.5, 1, 2, 4, 12, and 24 h after dosing and assayed for the prodrug and metabolite as described in Materials and Methods. Pharmacokinetic parameters were estimated using mean data from one male and one female in each group at each time point. AUC<sub>0-24</sub>, AUC from 0 to 24h; t<sub>1/2elim</sub>, elimination half-life; ND, not determined.

(See G. Painter et al., Evaluation of Hexadecyloxypropyl-9-R-[2-(Phosphonomethoxy)Propyl]-Adenine, CMX157, as a Potential Treatment for Human Immunodeficiency Virus Type 1 and Hepatitis B Virus Infections, Antimicrobial Agents and Chemotherapy 51, 3505-3509 (2007). )

## EXAMPLE 2

**[0104]** To examine the potential of CMX157 to associate directly with virus, concentrated HIV-1<sub>IIIB</sub> (approximately  $9.7 \times 10^{10}$  virus particles) is treated with 500 nM CMX157 or TFV for 2 hours. Following incubation, virus is pelleted to remove unbound compound, lysed with 70% ice cold methanol and centrifuged. Supernatants are analyzed in triplicate using LC/MS/MS (liquid chromatography/mass spectrometry). TFV, TFV mono- and diphosphate are separated by gradient, reverse phase, ion-pairing chromatography and detected by positive ion electrospray. The levels of CMX157 associated with the viral pellets ( $\approx 37,000$  molecules/virion) are much higher than the levels of TFV associated with viral pellets ( $\approx 100$  molecules/virion).

**[0105]** To evaluate the effect of exposing purified virus to drug on TCID<sub>50</sub>, concentrated HIV-1<sub>IIIB</sub> virus (approximately  $9.7 \times 10^{10}$  virus particles) is treated with 1000, 500, 250 or 125 nM CMX157 or TFV for 2 hours. As shown in **Table 5**, CMX157 consistently reduce viral replication 2-4 fold across this dose range while TFV has no discernible effect even at the highest dose.

Table 5: TCID<sub>50</sub> Determination of Treated HIV-1<sub>IIIB</sub>(2 hours)

Drug (nM)	CMX157 (Fold Decrease From VC*)			TFV (Fold Decrease From VC)		
	XTT Endpoint	RT Endpoint	P24 Endpoint	XTT Endpoint	RT Endpoint	P24 Endpoint
1000	1132 (4.0)	36227 (2.2)	7604 (4.8)	4529 (0)	64570 (1.3)	36227 (0)
500	1132 (4.0)	36227 (2.2)	7604 (4.8)	4529 (0)	81289 (0)	37328 (0)
250	1132 (4.0)	25588 (3.2)	10765 (3.4)	4529 (0)	72449 (1.1)	36227 (0)
125	1132 (4.0)	51172 (1.6)	9058 (4.0)	4027 (1.1)	72449 (1.1)	43056 (0)
0	4529	81289	36227	4529	81289	36227
*VC=vehicle control						

**[0106]** To determine the time dependence of compound incubation on loss of infectivity, concentrated HIV-1<sub>IIIB</sub> is treated with 500 nM CMX157 for 1, 15, 30, 60, and 120 minutes. The TCID<sub>50</sub> results of these assays are summarized in **Table 6**. CMX157 decreases infectivity following 1 minute incubation prior to centrifugation.

Table 6: TCID<sub>50</sub> Determination of Treated HIV-1<sub>IIIB</sub>

Time of Compound Removal	Untreated Virus			CMX157 500nM (Fold Decrease From VC*)		
	XTT Endpoint	RT Endpoint	P24 Endpoint	XTT Endpoint	RT Endpoint	P24 Endpoint
1 minute	4529	132749	36227	2014 (2.2)	25588 (5.2)	4529 (8.0)
15 minutes	4529	64570	36227	1132 (4.0)	18115 (3.6)	6398 (5.7)
30 minutes	4027	64570	36227	2014 (2.0)	22805 (2.8)	18115 (2.0)
60 minutes	4027	87303	36227	1600 (2.5)	25588 (3.4)	9058 (4.0)
120 minute	4529	81289	36227	1132 (4.0)	25588 (3.2)	6398 (5.7)
*VC=vehicle control						

**[0107]** In the second experiment to determine the dose effect of CMX157 treated HIV-1<sub>IIIB</sub> on infectivity, concentrated virus is incubated for 15 minutes with eight concentrations ranging from 0.039 to 125 nM of test material and TCID<sub>50</sub> values are measured by XTT, RT and p24. HDP-ACV is evaluated in parallel to determine if a lipid-nucleotide of similar structure but without HIV activity would have any effect in this assay. The TCID<sub>50</sub> results of these assays are summarized in **Table 7**.

**[0108]** Evaluation of CMX157 associated with HIV-1<sub>IIIB</sub> using lower concentrations of test material yielded a dose response indicating concentrations of 3.9 nM and greater resulted in reduced infectivity. The XTT and p24 endpoints for measuring TCID<sub>50</sub> yielded greater fold decreases in infectivity compared to the RT endpoint as might be expected for a NRTI in this system. HDP-ACV had no effect on infectious virus when incubated with HIV-1<sub>IIIB</sub> at the concentrations evaluated.

Table 7: TCID<sub>50</sub> Determination of Treated HIV-1<sub>IIIB</sub> (15 minutes)

Drug (nM)	CMX157 (Fold Decrease From VC*)			HDP-ACV (Fold Decrease From VC)		
	XTT Endpoint	RT Endpoint	P24 Endpoint	XTT Endpoint	RT Endpoint	P24 Endpoint
125	4027 (4.5)	64570 (2.5)	7604 (4.0)	18115 (0)	162566 (0)	21529 (1.4)
39.1	5082 (3.6)	64570 (2.5)	7604 (4.0)	16145 (1.1)	204659 (0)	30411 (0)
12.5	4529 (4.0)	102336 (1.6)	5383 (5.6)	18115 (0)	144887 (1.1)	36227 (0)
3.9	4529 (4.0)	102336 (1.6)	15207 (2.0)	20325 (0)	102336 (1.6)	30411 (0)
1.25	9058 (2.0)	102336 (1.6)	30411 (0)	16145 (1.1)	102336 (1.6)	21529 (1.4)
0.39	12795 (1.4)	102336 (1.6)	21529 (1.4)	20325 (0)	144887 (1.1)	30411 (0)
0.125	16145 (1.1)	144887 (1.1)	30411 (0)	16145 (1.1)	102336 (1.6)	36277 (0)
0.039	16145 (1.1)	157772 (1.0)	36337 (0)	18115 (0)	132749 (1.2)	30411 (0)
0	18115	162566	30411	18155	162566	30411
*VC= vehicle control						

**[0109]** Overall, these results indicate CMX157 associates directly with HIV and that this association reduces viral replication. Incubation of HIV with low nanomolar concentrations of CMX157 for short periods of time (1-15 minutes) resulted in decreased viral production *in vitro*. No effect on viral replication is seen for TFV or the lipid control, HDP-ACV. CMX157 may have advantages over TFV via this mechanism of cell targeting as any HIV exposed to CMX157 will then carry its own antiviral to whatever compartment or cell type it subsequently enters.

**[0110]** The mechanism suggested by the experiments presented here invokes direct association of the CMX157 lipid-TFV drug with HIV followed by delivery of CMX157 by the virus to the cell being infected. The data presented herein demonstrates a significant difference (approximate 300 fold) in the level of CMX157 directly associated with purified HIV versus TFV. Furthermore, pre-incubation of HIV with CMX157 inhibited replication of HIV in cells that are not exposed to drug except via the virus itself; pre-incubation of HIV with TFV has no inhibitory effect on subsequent HIV replication, consistent with the low levels of TFV associated with isolated virions.

**[0111]** This mechanism is distinct from inhibition of natural endogenous reverse transcription (NERT) within HIV virions. Inhibition of NERT has been demonstrated *in vitro* with high levels of AZT-triphosphate (10uM) or Nevirapine (NVP) and *in vivo* with NVP (Zhang 1996, Zhang 2006). While there could be an element of NERT inhibition when cells are treated with CMX157, this mechanism presumably requires formation of TFV-PP which should not occur within isolated virions.

### EXAMPLE 3

**[0112]** The anti-HIV-1 activity of CMX157 is evaluated in two-drug combination studies with twenty-four different FDA-approved anti-HIV inhibitors. Each two-drug combination is tested three times in CEM T-lymphocytic cells or MAGI-CCR5 cells acutely infected with the laboratory-adapted strain HIV-1<sub>IIIB</sub> or HIV-1<sub>Ba-L</sub>, respectively. Viral growth/inhibition is evaluated by measuring virus-induced cytopathic effects (CPE) in CEM cells or by  $\beta$ -galactosidase reporter gene induction in MAGI-CCR5 cells at the experimental endpoint. The cytotoxicity of each two-drug combination is also evaluated in parallel with the antiviral evaluations. The concentrations of CMX 157 used in these evaluations are selected in order to test a broad range of concentrations and to provide as complete a dose response curve as possible under the limitations of eight total concentrations. Similarly, the concentrations of lamivudine, abacavir, zidovudine, stavudine, zalcitabine, didanosine, emtricitabine, tenofovir, delavirdine, efavirenz, etravirine, nevirapine, amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, maraviroc, enfuvirtide, and raltegravir are selected to provide as complete of a dose response curve as possible under the limitations of five total concentrations. The "positive antagonism control" of d4T (stavudine) in combination with RBV was tested in parallel with each of the assays that were performed. Analysis of drug interactions for each of the two-drug combinations is performed using the Prichard and Shipman MacSynergy II three-dimensional model for statistical evaluation of combination assays. The results from these experiments are summarized in Table 8 and interpretation of the results is provided in Table 9.

**[0113]** For these studies, synergy is defined as drug combinations yielding synergy volumes greater than 50. Slightly synergistic activity and highly synergistic activity have been operationally defined as yielding synergy volumes of 50-100 and > 100, respectively. Additive drug interactions have synergy volumes in the range of -50 to 50, while synergy volumes between -50 and -100 are considered slightly antagonistic and those < -100 are highly antagonistic. When assessing

interactions at the 50% inhibitory concentrations ( $IC_{50}$ ) for the two drugs, the average dose response from three experiments for each two-drug combination is determined and the  $IC_{50}$  range for the two drugs is assessed as the two drug concentrations that bracketed the  $IC_{50}$  value (data not shown). If one of the concentrations for a particular drug yields an average percent inhibition of  $50\% \pm 5\%$ , then this concentration plus the two on either side were included in the  $IC_{50}$  range. Subsequently, the interactions within the  $IC_{50}$  range of the two drugs were operationally defined as: 1) interactions with synergy volumes  $> 20$  is considered synergistic; 2) interactions with synergy volumes in the range of  $-20$  to  $20$  are considered additive; and 3) interactions with synergy volumes  $< -20$  are considered antagonistic.

**[0114]** Overall, CMX-157 is determined to have additive or synergistic interactions for all two-drug combinations performed with FDA-approved antiretroviral drugs. None of the interactions is found to be antagonistic. This conclusion of additive to synergistic interactions for all combinations is also reached when assessing the interactions at the  $IC_{50}$  range of the two drugs from each combination. In contrast, the positive antagonism control of stavudine in combination with ribavirin resulted in antagonistic interactions as expected.

**Table 8 Antiviral Efficacy of CMX157 in Combination with Approved Antiretrovirals in CEM and MAGI-CCR5 Cells (95% Confidence Values)**

Compound	Synergy / Antagonism Volume (nM <sup>2</sup> %, μM <sup>2</sup> % or nMμM%) <sup>1</sup>			Mean Synergy / Antagonism Volume (nM <sup>2</sup> %, μM <sup>2</sup> % or nMμM%; n=3) <sup>2</sup>
	Result 1	Result 2	Result 3	
Nucleoside Reverse Transcriptase Inhibitors (NRTI)				
Lamivudine (3TC)	87.5 / -42.6	51.8/0	79.0 / 0	69.8 / -11.3
Abacavir (ABC)	25.1 / -35.8	0 / -2.32	19.7 / -12.1	14.9 / -16.7
Zidovudine (AZT)	5.01 / -67.8	32.7 / 0	0 / -0.77	11.5 / -21.7
Stavudine (d4T)	4.47 / 0	40.6 / 0	0.39 / -1.83	15.2 / -0.61
Zalcitabine (ddC)	154/0	80.0 / 0	131 / -15.9	122/-5.29
Didanosine (ddI)	3.38 / -1.01	3.04/0	29.6 / 0	12.0 / -0.34
Emtricitabine (FTC)	61.5 / 0	72.0/0	84.1 / 0	72.5 / 0
Tenofovir (TFV)	17.6 / -0.53	37.2 / 0	30.3 / 0	28.4 / -0.18
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)				
Delavirdine (DLV)	152 / 0	68.4 / 0	1.01 / -2.58	72.9 / 0
Efavirenz (EFV)	85.7 / 0	80.6 / 0	43.2 / 0	69.8 / 0
Etravirine (ETV)	34.9 / -0.75	106/0	67.4 / -0.87	69.0 / -0.29
Nevirapine (NVP)	74.1/0	41.5 / 0	0 / 0	38.5 / 0
Protease Inhibitors (PI)				
Amprenavir (APV)	104 / 0	43.1 / 0	7.31 / 0	51.4 / 0
Atazanavir (ATV)	104/0	67.4 / 0	12.7 / -0.72	61.5 / -0.24
Darunavir (DRV)	109/0	11.5 / -2.31	9.48 / 0	43.2 / -0.54
Indinavir (IDV)	78.7 / -0.56	62.7 / 0	17.6/0	53.0 / -0.19
Lopinavir (LPV)	78.8 / -0.31	28.3 / 0	59.8 / -0.12	55.6 / -0.14
Nelfinavir (NFV)	32.1 / 0	85.1 / 0	125 / 0	80.9 / 0
Ritonavir (RTV)	47.5 / 0	38.0 / 0	116 / -2.61	66.4 / 0
Saquinavir (SQV)	123 / -2.54	8.35 / -0.81	3.93 / 0	45.2 / -1.12
Tipranavir (TPV)	110/0	29.4 / -8.60	16.8 / 0	52.2/-2.87
Entry Inhibitors				
Maraviroc (MVC) <sup>3</sup>	145 / -3.82	14.1 / -3.12	96.6 / 0	85.3 / -2.31
Enfuvirtide (T-20)	0 / 0	3.05 / 0	0 / 0	1.02 / 0



(continued)

**Integrase Inhibitor**

Raltegravir (RAL)	18.4 / 0	1.92/0	82.6 / 0	34.3 / 0
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<sup>1</sup>The MacSynergy II program takes the raw data from individual experiments and calculates a positive (synergy) or negative (antagonism) value for each drug-drug combination. Positive values are summed to give a Volume of Synergy and negative values are summed to give a Volume of Antagonism (both values are reported for each experiment).

<sup>2</sup>The Antiviral Synergy Plot (95%) datasets from multiple experiments (n = 3) are combined and arithmetic means are calculated for each drug-drug concentration. The positive and negative values are individually summed to respectively give Mean Volumes for synergistic and antagonistic interactions.

<sup>3</sup>The antiviral efficacy results of CMX157 in combination with Maraviroc were performed in MAGI-CCR5 cells. All other evaluations were performed in CEM-SS cells.

**Table 9 Interpretation of the MacSynergy Analysis for the Antiviral Efficacy of CMX157 in Combination with Approved Antiretroviral Drugs**

Antiretroviral Drug	Interpretation of Antiviral Results
<b>Nucleoside Reverse Transcriptase Inhibitors (NRTI)</b>	
Lamivudine (3TC)	Slightly Synergistic
Abacavir (ABC)	Additive
Zidovudine (AZT)	Additive
Stavudine (d4T)	Additive
Zalcitabine (ddC)	Highly Synergistic
Didanosine (ddI)	Additive
Emtricitabine (FTC)	Slightly Synergistic
Tenofovir (TFV)	Additive
<b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)</b>	
Delavirdine (DLV)	Slightly Synergistic
Efavirenz (EFV)	Slightly Synergistic
Etravirine (ETV)	Slightly Synergistic
Nevirapine (NVP)	Additive
<b>Protease Inhibitors (PI)</b>	
Amprenavir (APV)	Slightly Synergistic
Atazanavir (ATV)	Slightly Synergistic
Darunavir (DRV)	Additive
Indinavir (IDV)	Slightly Synergistic
Lopinavir (LPV)	Slightly Synergistic
Nelfinavir (NFV)	Slightly Synergistic
Ritonavir (RTV)	Slightly Synergistic
Saquinavir (SQV)	Additive
Tipranavir (TPV)	Slightly Synergistic
<b>Entry Inhibitors</b>	
Maraviroc (MVC)	Slightly Synergistic
Enfuvirtide (T-20)	Additive

(continued)

<b>Integrase Inhibitor</b>	
Raltegravir (RAL)	Additive
<b>Positive Antagonism Control (CEM-SS Cells)</b>	
Stavudine/Ribavirin (d4T/RBV)	Highly Antagonistic at expected concentrations
<b>Positive Antagonism Control (MAGI-CCR5 Cells)</b>	
Stavudine/Ribavirin (d4T/RBV)	Highly Antagonistic at expected concentrations

[0115] No antagonistic interactions were observed within the concentration ranges examined for antiviral efficacy between CMX157 and the twenty-four FDA-approved antiretroviral drugs. A highly synergistic interaction is observed between CMX157 and zalcitabine, and slightly synergistic interactions were observed with lamivudine, emtricitabine, delavirdine, efavirenz, etravirine,, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc, suggesting possible beneficial interactions with these drugs. CMX157 interactions with the remaining drugs resulted in strictly additive results. In contrast, the positive antagonism control of stavudine in combination with Ribavirin exhibited a highly antagonistic interaction in all experiments (mean antagonism volume = -330  $\mu\text{M}^2\%$  in CEM cells and -111  $\mu\text{M}^2\%$  in MAGI-R5 cells). Therefore, the overall interpretation of these data suggest that antagonism of the antiviral effects of the twenty-four FDA-approved antiretroviral drugs evaluated in this study should not be a problematic issue associated with the use of CMX157 in a clinical setting.

[0116] It is important to note there was no evidence of synergistic cytotoxicity within the drug concentrations examined for CMX157 (10  $\mu\text{M}$  = highest test concentration). This is not unexpected because none of the drugs are cytotoxic within the concentration ranges evaluated. Much higher concentrations of all drugs (around the  $\text{TC}_{50}$  concentration) would be required to correctly examine potential synergistic cytotoxicity interactions. However, it is important to document there are no notable synergistic cytotoxicities observed at concentrations where the FDA-approved drugs display potent antiviral properties.

#### Example 4

[0117] The signature mutation for tenofovir (TFV) is K65R, which is generally associated with a 2 to 4 fold increase in  $\text{IC}_{50}$  for tenofovir and lack of clinical response to Viread. *In vitro* studies designed to select CMX157 resistant mutants use wild-type HIV-1 as the primary inoculum and TFV as a positive control. These studies are conducted by serial passage of HIV-1<sub>IIIB</sub> and HIV-1RF in CEM-SS cells using increasing concentrations of TFV or CMX157. Drug levels are increased following detection of viral growth at each passage using procedures known to one skilled in the art. Upon completion of each passage, the reverse transcriptase coding region of the viral genome is sequenced to identify any possible resistance-associated mutations that may have emerged within the virus pool.

[0118] As show in Tables 10 and 11, there is no resistance to CMX157 through 9 passages. In contrast, K65R was selected by TFV by passage 8. These data indicates it may be more difficult for HIV to develop resistance to CMX157 than to TFV.

**Table 10: Passaging of HIV-1<sub>IIIB</sub> in CMX157**

Passage	CMX157 Passaging Concentration (Fold above $\text{IC}_{50}$ )	Day of Peak Virus Production <sup>a</sup> (RT activity)	Mutations Observed in RT of Passaged Virus	Comments
1	300 nM (2X $\text{IC}_{50}$ )	Day 6 (23,615 cpm)	None	Robust virus replication observed
2	600 nM (4X $\text{IC}_{50}$ )	Day 6 (6,706 cpm)	None	Reduced virus replication observed
3	900 nM (6X $\text{IC}_{50}$ )	Day 14 (11,364 cpm)	None	Moderate virus replication observed
4	1,200 nM (8X $\text{IC}_{50}$ )	Day 6 (34,440 cpm)	None	Robust virus replication observed

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(continued)

Passage	CMX157 Passaging Concentration (Fold above IC <sub>50</sub> )	Day of Peak Virus Production <sup>a</sup> (RT activity)	Mutations Observed in RT of Passaged Virus	Comments
5	1,800 nM (12X IC <sub>50</sub> )	Day 6 (14,061 cpm)	None	Moderate virus replication observed
6	2,400 nM (16X IC <sub>50</sub> )	Day 7 (9,933 cpm)	T2151 mix (minor population)	Low-level to moderate virus replication observed; minor mix of T2151 unlikely to be associated with resistance to CMX157 (not observed in passage 7)
7	2,800 nM (19X IC <sub>50</sub> )	Day 5 (1,900 cpm)	None	Low-level virus replication observed through 16 days in culture; continue with passage 8 using same concentration in order to allow virus to grow out
8	2,800 nM (19X IC <sub>50</sub> )	Day 9 (18,638 cpm)	Minor, mixed populations observed: E122K, T2001, Q207E, P272A, R277K, I293V, P294Q, E297K, and T400A	Relatively robust virus replication observed; minor mixes of amino acids observed unlikely to be associated with resistance to CMX157, these changes are reported based on small peak heights observed in the chromatograms, however most of these small peaks are likely to be artifacts of the sequencing
9	5,600 nM (36X IC <sub>50</sub> )	Day 11 (1,585 cpm)	Minor, Mixed Populations observed: E122K, D123E, T200I, Q207E, R211K, P272A, R277K, I293V, P294Q, E297K, I375V, T400A, N519S, A554T	Low level virus replication observed through 13 days in culture; RT activity peaked at day 11 and dropped off on days 12 and 13. Therefore, day 11 supernatant was used, even though the RT activity is still relatively low at 1,585 cpm. Minor mixes of amino acids present; unlikely to be associated with resistance to CMX157
<sup>a</sup> Day post-infection when greatest level of virus was observed based on RT activity <sup>b</sup> minor = mutation is minor population in mix; major = mutation is major population; equal = equal peak heights N/A = not applicable (virus replication not observed or RT not sequenced)				

Table 11: Passaging of HIV-1<sub>IIIIB</sub> in Tenofovir

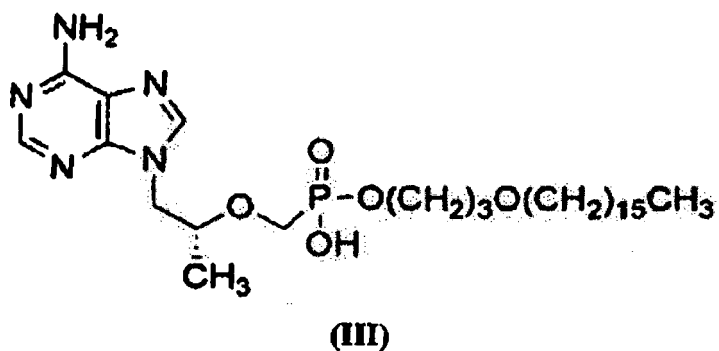
Passage	Tenofovir Passaging Concentration (Fold above IC <sub>50</sub> )	Day of Peak Virus Production <sup>a</sup> (RT activity)	Mutations Observed in RT of Passaged Virus <sup>b</sup>	Comments
1	10 µM (2X IC <sub>50</sub> )	Day 6 (3,525 cpm)	None	Low-level virus replication observed
2	20 µM (4X IC <sub>50</sub> )	Day 7 (2,016 cpm)	None	Low-level virus replication observed
3	30 µM (6X IC <sub>50</sub> )	Day 14 (2,062 cpm)	None	Low-level virus replication observed

(continued)

Passage	Tenofovir Passaging Concentration (Fold above IC <sub>50</sub> )	Day of Peak Virus Production <sup>a</sup> (RT activity)	Mutations Observed in RT of Passaged Virus <sup>b</sup>	Comments
4	40 $\mu$ M (8X IC <sub>50</sub> )	Day 6 (3,109 cpm)	None	Low-level virus replication observed
5	40 $\mu$ M (8X IC <sub>50</sub> )	Day 14 (1,788 cpm)	None	Low-level virus replication observed; continue with passage 6 using same concentration in order to allow virus to grow out
6	40 $\mu$ M (8X IC <sub>50</sub> )	Day 19 (23,508)	None	Robust virus replication observed; apparent significant increase in replication compared to passages 1-5
7	45 $\mu$ M (9X IC <sub>50</sub> )	Day 7 (24,408 cpm)	E300D mix (minor population)	Robust virus replication observed; minor mix of E300D unlikely to be associated with resistance to tenofovir (not observed in passage 8)
8	50 $\mu$ M (10X IC <sub>50</sub> )	Day 9 (57,455 cpm)	E404D mix (minor)G436E mix (minor)	Robust virus replication observed; E404D and G436E changes possibly associated with resistance selection by tenofovir
9	55 $\mu$ M (11X IC <sub>50</sub> )	Day 11 (25,458 cpm)	<b>K65R mix (equal)</b> E404D mix (major)G436E mix (minor)	Robust virus replication observed; <b>prototypical tenofovir resistance mutation K65R starting to emerge;</b> E404D and G436E mutations appear to be associated with tenofovir resistance
10	60 $\mu$ M (12X IC <sub>50</sub> )	Day 7 (31,549 cpm)	<b>K65R mix (major)</b> E404D mix (minor)G436E mix (minor)	Robust virus replication observed; <b>prototypical tenofovir resistance mutation K65R = major population;</b> E404D and G436E mutations appear to be associated with tenofovir resistance
<sup>a</sup> Day post-infection when greatest level of virus was observed based on RT activity <sup>b</sup> minor = mutation is minor population in mix; major = mutation is major population; equal = equal peak heights N/A = not applicable (virus replication not observed or RT not sequenced)				

## Claims

1. An antiviral compound of Formula III:



in combination with at least one additional antiviral active agent selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc, for use in a method of treating a subject for human immunodeficiency virus (HIV) infection, wherein the subject has not been previously administered an antiviral active agent for said HIV, the method comprising administering to said subject an amount of the compound, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, effective to treat the HIV infection and inhibit the development of resistance to said compound in the subject.

2. The compound for use in the method of claim 1, wherein said subject is further infected with HBV, and said antiviral compound and at least one additional antiviral active agent is administered in an amount effective to treat both said HBV and HIV.

3. An antiviral compound of Formula III, as defined in claim 1, in combination with at least one additional antiviral active agent selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc, for use in a method of treating a subject for human immunodeficiency virus (HIV) infection, wherein said subject has developed resistance or a toxic response to at least one other antiviral compound in response to prior administration of said at least one other antiviral compound to said subject for said HIV infection, the method comprising administering to said subject an amount of the compound of Formula III, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, effective to treat the HIV infection and inhibit the development of resistance to said compound in said subject.

4. The compound for use in the method of claim 3 wherein said subject is further infected with HBV, and said antiviral compound is administered in an amount effective to treat both said HBV and HIV.

5. A pharmaceutical composition consisting of:

- (a) a first antiviral compound of Formula III as defined in claim 1, or a pharmaceutically acceptable salt, or a stereoisomer, a diastereomer, an enantiomer or racemate thereof;
- (b) one or more additional antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc; and
- (c) a pharmaceutically acceptable carrier.

6. The composition of claim 5, wherein:

- (i) the composition is in unit dose form; and/or
- (ii) the composition is in oral administration form.

7. An antiviral compound of Formula III, as defined in claim 1, and one or more antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc, for use in a method for inhibiting sexual transmission of HIV, the method comprising topically applying to the skin or epithelial tissue of a human a therapeutically effective amount of a composition comprising the compound, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof.

8. The compound for use in the method of claim 7 wherein:

- (i) the composition is applied intravaginally, intrarectally or to the external male genitalia; and/or
- (ii) the composition is in the form of a cream, lotion, gel, or foam; or in the form of an intra-vaginal pill, an intra-rectal pill, or a suppository; and/or
- (iii) the composition can be topically applied by release from an intravaginal device selected from a vaginal ring, a vaginal sponge, a diaphragm, or a cervical cap; or wherein the composition is topically applied from the exterior surface of a condom or vaginal applicator; and/or
- (iv) the composition further comprises a viracide effective against viral infections other than HIV; a spermicide; and/or a combination thereof; and/or
- (v) the composition further comprises a lubricant.

9. A topical composition in the form of a cream, lotion, gel, or foam, comprising an antiviral compound of Formula III as defined in claim 1, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, wherein

- (i) the composition further comprises one or more additional anti-HIV agents; or
- (ii) the composition further comprises a viracide effective against viral infections other than HIV; or
- (iii) the composition further comprises a spermicide; or
- (iv) the composition further comprises a lubricant; or
- (v) the composition further comprises one or more additional antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc.

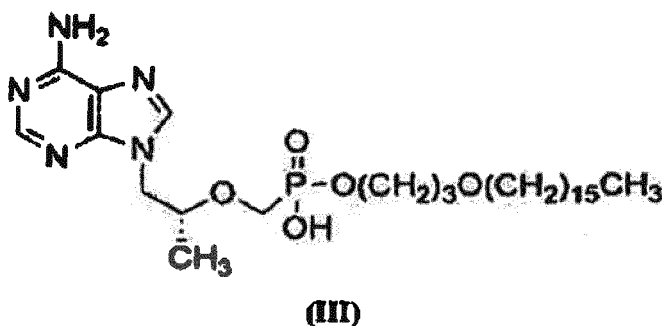
10. A device for inhibiting the sexual transmission of HIV comprising: a) a barrier structure for insertion into the vaginal cavity, and b) a composition comprising an antiviral compound of Formula III as defined in claim 1, or a pharmaceutically acceptable salt, a stereoisomer, a diastereomer, an enantiomer or racemate thereof, and one or more additional antiviral active agents selected from the group consisting of lamivudine, zalcitabine, emtricitabine, delavirdine, efavirine, etravirine, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and maraviroc.

11. The device of claim 10, wherein:

- (i) the barrier structure is a vaginal sponge, diaphragm, cervical cap, or condom; and/or
- (ii) the device further comprises additional anti-HIV agents, a viracide effective against viral infections other than HIV, and/or a spermicide.

## Patentansprüche

1. Antivirale Verbindung der Formel III:



- in Kombination mit wenigstens einem zusätzlichen antiviralen Wirkstoff, ausgewählt aus der Gruppe bestehend aus Lamivudin, Zalcitabin, Emtricitabin, Delavirdin, Efavirine, Etravirin, Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Tipranavir und Maraviroc, zur Verwendung in einem Verfahren zum Behandeln eines Probanden auf eine Infektion mit dem humanen Immundefizienzvirus (HIV), wobei dem Probanden zuvor kein antiviraler Wirkstoff für das HIV verabreicht worden ist, wobei das Verfahren das Verabreichen einer Menge der Verbindung oder eines pharmazeutisch verträglichen Salzes, eines Stereoisomers, eines Diastereomers, eines Enantiomers oder Racemats davon an den Probanden umfasst, die zum Behandeln der HIV-Infektion und Hemmen der Entwicklung einer Resistenz gegen die Verbindung in dem Probanden wirksam ist.
2. Verbindung zur Verwendung in dem Verfahren nach Anspruch 1, wobei der Proband außerdem mit HBV infiziert ist und die antivirale Verbindung und wenigstens ein zusätzlicher antiviraler Wirkstoff in einer Menge verabreicht wird, die zum Behandeln von sowohl dem HBV als auch HIV wirksam ist.
3. Antivirale Verbindung der Formel III, wie in Anspruch 1 definiert, in Kombination mit wenigstens einem zusätzlichen antiviralen Wirkstoff, ausgewählt aus der Gruppe bestehend aus Lamivudin, Zalcitabin, Emtricitabin, Delavirdin,

Efavirnez, Etravirin, Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Tipranavir und Maraviroc, zur Verwendung in einem Verfahren zum Behandeln eines Probanden auf eine Infektion mit dem humanen Immundefizienzvirus (HIV), wobei der Proband eine Resistenz oder eine toxische Reaktion gegen wenigstens eine andere antivirale Verbindung als Reaktion auf eine vorherige Verabreichung der wenigstens einen anderen antiviralen Verbindung an den Probanden für die HIV-Infektion entwickelt hat, wobei das Verfahren das Verabreichen einer Menge der Verbindung der Formel III, oder eines pharmazeutisch verträglichen Salzes, eines Stereoisomers, eines Diastereomers, eines Enantiomers oder Racemats davon, an den Probanden umfasst, die zum Behandeln der HIV-Infektion und Hemmen der Entwicklung einer Resistenz gegen die Verbindung in dem Probanden wirksam ist.

4. Verbindung zur Verwendung in dem Verfahren nach Anspruch 3, wobei der Proband außerdem mit HBV infiziert ist und die antivirale Verbindung in einer Menge verabreicht wird, die zum Behandeln von sowohl dem HBV als auch HIV wirksam ist.

5. Pharmazeutische Zusammensetzung bestehend aus:

- (a) einer ersten antiviralen Verbindung der Formel III wie in Anspruch 1 definiert, oder einem pharmazeutisch verträglichem Salz, oder einem Stereoisomer, einem Diastereomer, einem Enantiomer oder Racemat davon;
- (b) einem oder mehreren zusätzlichen antiviralen Wirkstoffen, ausgewählt aus der Gruppe bestehend aus Lamivudin, Zalcitabin, Emtricitabin, Delavirdin, Efavirnez, Etravirin, Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Tipranavir und Maraviroc; und
- (c) einem pharmazeutisch verträglichen Träger.

6. Zusammensetzung nach Anspruch 5, wobei:

- (i) die Zusammensetzung in Einheitsdosisform vorliegt, und/oder
- (ii) die Zusammensetzung in oraler Verabreichungsform vorliegt.

7. Antivirale Verbindung der Formel III, wie in Anspruch 1 definiert, und ein oder mehrere antivirale Wirkstoffe, ausgewählt aus der Gruppe bestehend aus Lamivudin, Zalcitabin, Emtricitabin, Delavirdin, Efavirnez, Etravirin, Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Tipranavir und Maraviroc, zur Verwendung in einem Verfahren zum Hemmen der sexuellen Übertragung von HIV, wobei das Verfahren das topische Anwenden einer therapeutisch wirksamen Menge einer Zusammensetzung, umfassend die Verbindung, oder ein pharmazeutisch verträgliches Salz, ein Stereoisomer, ein Diastereomer, ein Enantiomer oder Racemat davon, auf die Haut oder Epithelgewebe eines Menschen umfasst.

8. Verbindung zur Verwendung in dem Verfahren nach Anspruch 7, wobei:

- (i) die Zusammensetzung intravaginal, intrarektal oder auf die äußeren männlichen Genitalien angewandt wird; und/oder
- (ii) die Zusammensetzung in Form einer Creme, einer Lotion, eines Gels oder eines Schaums; oder in Form einer intravaginalen Pille, einer intrarektalen Pille oder eines Zäpfchens vorliegt; und/oder
- (iii) die Zusammensetzung durch Freisetzung aus einer intravaginalen Vorrichtung, ausgewählt aus einem Vaginalring, einem Vaginalschwamm, einem Diaphragma oder einer Portiokappe, topisch angewandt werden kann; oder wobei die Zusammensetzung von der äußeren Oberfläche eines Kondoms oder Vaginalapplikators topisch angewandt wird; und/oder
- (iv) die Zusammensetzung außerdem ein Viruzid, das gegen andere Virusinfektionen als HIV wirksam ist; ein Spermizid; und/oder eine Kombination davon umfasst; und/oder
- (v) die Zusammensetzung außerdem ein Gleitmittel umfasst.

9. Topische Zusammensetzung in Form einer Creme, einer Lotion, eines Gels oder eines Schaums, umfassend eine antivirale Verbindung der Formel III wie in Anspruch 1 definiert, oder ein pharmazeutisch verträgliches Salz, ein Stereoisomer, ein Diastereomer, ein Enantiomer oder Racemat davon, wobei

- (i) die Zusammensetzung außerdem einen oder mehrere zusätzliche Anti-HIV-Wirkstoffe umfasst; oder
- (ii) die Zusammensetzung außerdem ein Viruzid, das gegen andere Virusinfektionen als HIV wirksam ist, umfasst; oder
- (iii) die Zusammensetzung außerdem ein Spermizid umfasst; oder

- (iv) die Zusammensetzung außerdem ein Gleitmittel umfasst; oder  
 (v) die Zusammensetzung außerdem einen oder mehrere zusätzliche antivirale Wirkstoffe, ausgewählt aus der Gruppe bestehend aus Lamivudin, Zalcitabin, Emtricitabin, Delavirdin, Efavirnez, Etravirin, Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Tipranavir und Maraviroc, umfasst.

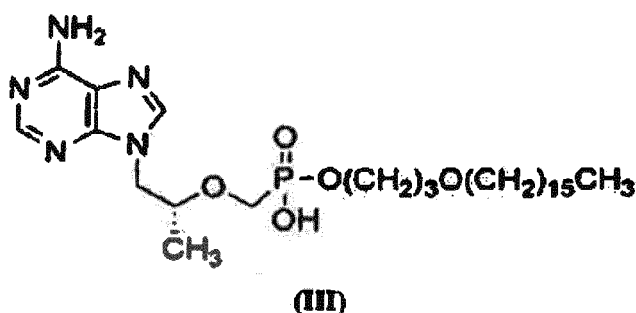
10. Vorrichtung zum Hemmen der sexuellen Übertragung von HIV, umfassend: a) eine Barrierestruktur zum Einsetzen in die Vaginalhöhle, und b) eine Zusammensetzung umfassend eine antivirale Verbindung der Formel III wie in Anspruch 1 definiert, oder ein pharmazeutisch verträgliches Salz, ein Stereoisomer, ein Diastereomer, ein Enantiomer oder Racemat davon, und einen oder mehrere zusätzliche antivirale Wirkstoffe, ausgewählt aus der Gruppe, bestehend aus Lamivudin, Zalcitabin, Emtricitabin, Delavirdin, Efavirnez, Etravirin, Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Tipranavir und Maraviroc.

11. Vorrichtung nach Anspruch 10, wobei:

- (i) die Barrierestruktur ein Vaginalschwamm, ein Diaphragma, eine Portiokappe oder ein Kondom ist; und/oder  
 (ii) die Vorrichtung außerdem zusätzliche Anti-HIV-Wirkstoffe, ein gegen andere Virusinfektionen als HIV wirksames Viruzid und/oder ein Spermizid umfasst.

## Revendications

1. Composé antiviral de formule III :



en association avec au moins un agent actif antiviral additionnel choisi dans le groupe constitué de la lamivudine, de la zalcitabine, de l'emtricitabine, de la delavirdine, de l'efavirenz, de l'étravirine, de l'amprénavir, de l'atazanavir, de l'indinavir, du lopinavir, du nelfinavir, du ritonavir, du tipranavir et du maraviroc, pour utilisation dans un procédé de traitement d'un sujet pour une infection par le virus de l'immunodéficience humaine (VIH), dans lequel le sujet n'a pas reçu préalablement d'agent actif antiviral pour ledit VIH, le procédé comprenant l'administration audit sujet d'une quantité du composé, ou d'un sel, d'un stéréoisomère, d'un diastéréomère, d'un énantiomère ou d'un racémate pharmaceutiquement acceptable de celui-ci, efficace pour traiter l'infection par le VIH et inhiber le développement d'une résistance audit composé chez le sujet.

2. Composé pour utilisation dans le procédé selon la revendication 1, dans lequel ledit sujet est en outre infecté par le VHB, et ledit composé antiviral et au moins un agent actif antiviral additionnel est administré en une quantité efficace pour traiter à la fois ledit VHB et ledit VIH.

3. Composé antiviral de formule III, tel que défini dans la revendication 1, en association avec au moins un agent actif antiviral additionnel choisi dans le groupe constitué de la lamivudine, de la zalcitabine, de l'emtricitabine, de la delavirdine, de l'efavirenz, de l'étravirine, de l'amprénavir, de l'atazanavir, de l'indinavir, du lopinavir, du nelfinavir, du ritonavir, du tipranavir et du maraviroc, pour utilisation dans un procédé de traitement d'un sujet pour une infection par le virus de l'immunodéficience humaine (VIH), dans lequel ledit sujet a développé une résistance ou une réponse toxique à au moins un autre composé antiviral en réponse à une administration préalable dudit au moins un autre composé antiviral audit sujet pour ladite infection par le VIH, le procédé comprenant l'administration audit sujet d'une quantité du composé de formule III, ou d'un sel, d'un stéréoisomère, d'un diastéréomère, d'un énantiomère ou d'un racémate pharmaceutiquement acceptable de celui-ci, efficace pour traiter l'infection par le VIH et inhiber



le développement d'une résistance audit composé chez ledit sujet.

4. Composé pour utilisation dans le procédé selon la revendication 3 dans lequel ledit sujet est en outre infecté par le VHB, et ledit composé antiviral est administré en une quantité efficace pour traiter à la fois ledit VHB et ledit VIH.

5. Composition pharmaceutique constituée de :

- (a) un premier composé antiviral de formule III tel que défini dans la revendication 1, ou un sel ou un stéréoisomère, un diastéréomère, un énantiomère ou un racémate pharmaceutiquement acceptable de celui-ci ;
- (b) un ou plusieurs agents actifs antiviraux additionnels choisis dans le groupe constitué de la lamivudine, de la zalcitabine, de l'emtricitabine, de la delavirdine, de l'éfavirenz, de l'étravirine, de l'amprénavir, de l'atazanavir, de l'indinavir, du lopinavir, du nelfinavir, du ritonavir, du tipranavir et du maraviroc ; et
- (c) un support pharmaceutiquement acceptable.

6. Composition selon la revendication 5, dans lequel :

- (i) la composition est sous une forme posologique unitaire ; et/ou
- (ii) la composition est sous une forme d'administration orale.

7. Composé antiviral de formule III, tel que défini dans la revendication 1, et un ou plusieurs agents actifs antiviraux choisis dans le groupe constitué de la lamivudine, de la zalcitabine, de l'emtricitabine, de la delavirdine, de l'éfavirenz, de l'étravirine, de l'amprénavir, de l'atazanavir, de l'indinavir, du lopinavir, du nelfinavir, du ritonavir, du tipranavir et du maraviroc, pour utilisation dans un procédé d'inhibition de la transmission sexuelle du VIH, le procédé comprenant l'application topique sur la peau ou le tissu épithélial d'un être humain d'une quantité thérapeutiquement efficace d'une composition comprenant le composé, ou un sel, un stéréoisomère, un diastéréomère, un énantiomère ou un racémate pharmaceutiquement acceptable de celui-ci.

8. Composé pour utilisation dans le procédé selon la revendication 7 dans lequel :

- (i) la composition est appliquée par voie intravaginale, par voie intrarectale ou sur les organes génitaux externes de l'homme ; et/ou
- (ii) la composition se présente sous la forme d'une crème, d'une lotion, d'un gel ou d'une mousse ; ou sous la forme d'une pilule intravaginale, d'une pilule intra-rectale ou d'un suppositoire ; et/ou
- (iii) la composition peut être appliquée par voie topique par libération à partir d'un dispositif intravaginal choisi parmi un anneau vaginal, une éponge vaginale, un diaphragme ou une cape cervicale ; ou dans lequel la composition est appliquée par voie topique à partir de la surface extérieure d'un préservatif ou d'un applicateur vaginal ; et/ou
- (iv) la composition comprend en outre un virucide efficace contre les infections virales autres que le VIH ; un spermicide ; et/ou une combinaison de ceux-ci ; et/ou
- (v) la composition comprend en outre un lubrifiant.

9. Composition topique sous la forme d'une crème, d'une lotion, d'un gel ou d'une mousse, comprenant un composé antiviral de formule III tel que défini dans la revendication 1, ou un sel, un stéréoisomère, un diastéréomère, un énantiomère ou un racémate pharmaceutiquement acceptable de celui-ci, dans laquelle

- (i) la composition comprend en outre un ou plusieurs agents anti-VIH additionnels ; ou
- (ii) la composition comprend en outre un virucide efficace contre les infections virales autres que le VIH ; ou
- (iii) la composition comprend en outre un spermicide ; ou
- (iv) la composition comprend en outre un lubrifiant ; ou
- (v) la composition comprend en outre un ou plusieurs agents actifs antiviraux additionnels choisis dans le groupe constitué de la lamivudine, de la zalcitabine, de l'emtricitabine, de la delavirdine, de l'éfavirenz, de l'étravirine, de l'amprénavir, de l'atazanavir, de l'indinavir, du lopinavir, du nelfinavir, du ritonavir, du tipranavir et du maraviroc.

10. Dispositif permettant d'inhiber la transmission sexuelle du VIH comprenant : a) une structure formant barrière à insérer dans la cavité vaginale, et b) une composition comprenant un composé antiviral de formule III tel que défini dans la revendication 1, ou un sel, un stéréoisomère, un diastéréomère, un énantiomère ou un racémate pharma-

ceutiquement acceptable de celui-ci, et un ou plusieurs agents actifs antiviraux additionnels choisis dans le groupe constitué de la lamivudine, de la zalcitabine, de l'emtricitabine, de la delavirdine, de l'éfavirenz, de l'étravirine, de l'amprénavir, de l'atazanavir, de l'indinavir, du lopinavir, du nelfinavir, du ritonavir, du tipranavir et du maraviroc.

5     **11.** Dispositif selon la revendication 10, dans lequel :

(i) la structure formant barrière est une éponge vaginale, un diaphragme, une cape cervicale ou un préservatif ;  
et/ou

10     (ii) le dispositif comprend en outre des agents anti-VIH additionnels, un virucide efficace contre les infections virales autres que le VIH et/ou un spermicide.

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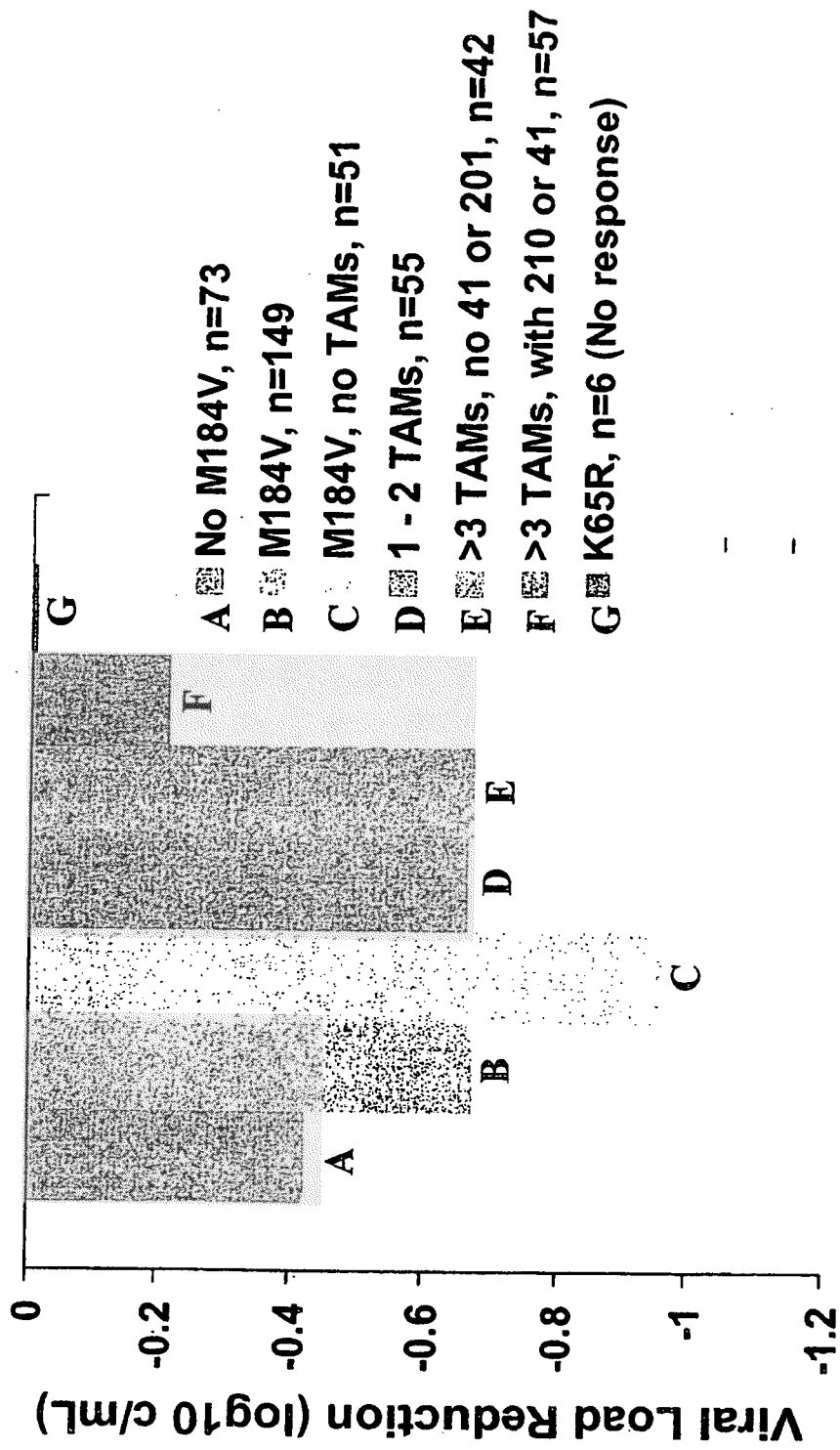
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**Figure 1**

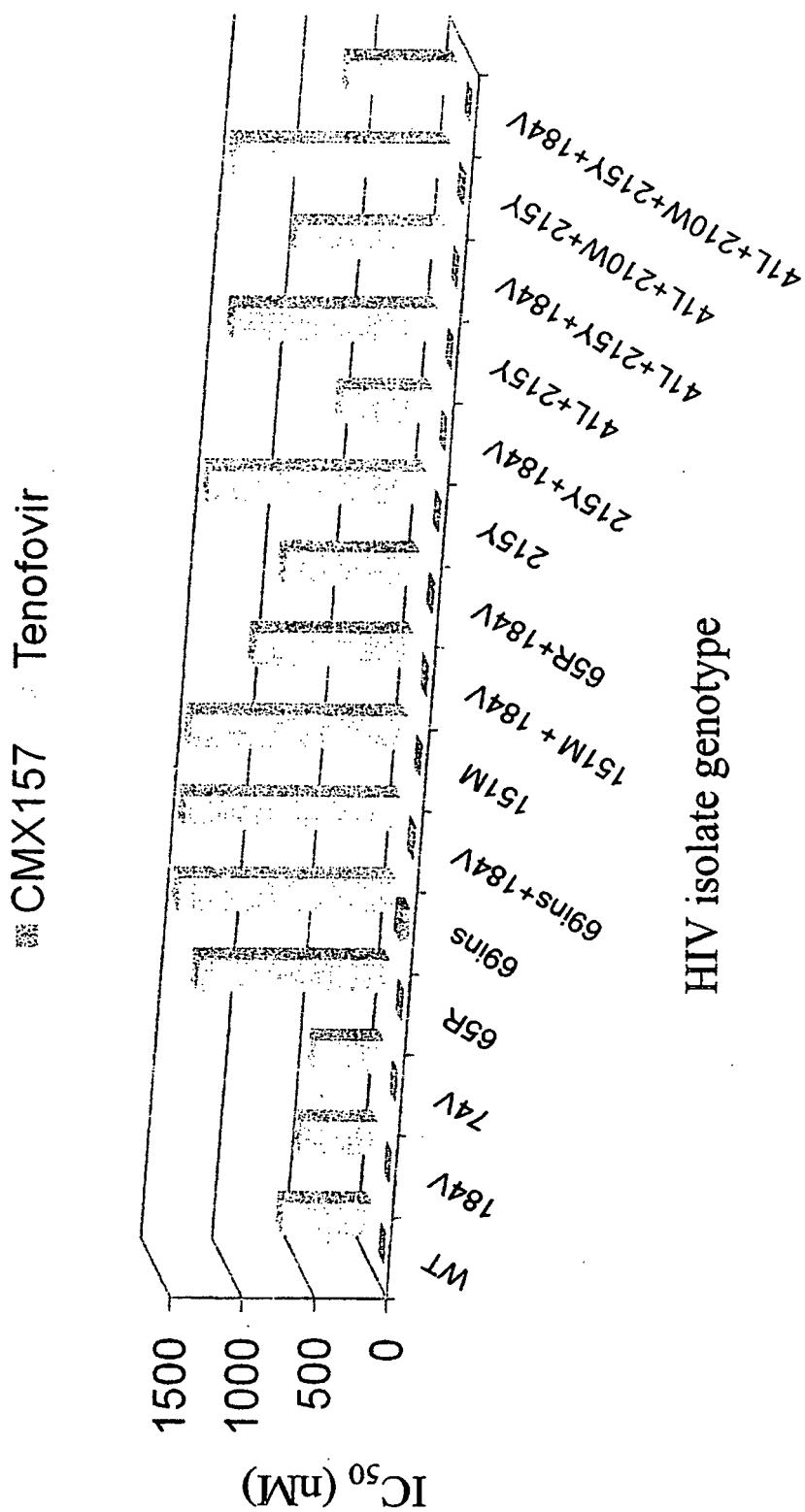


Figure 2

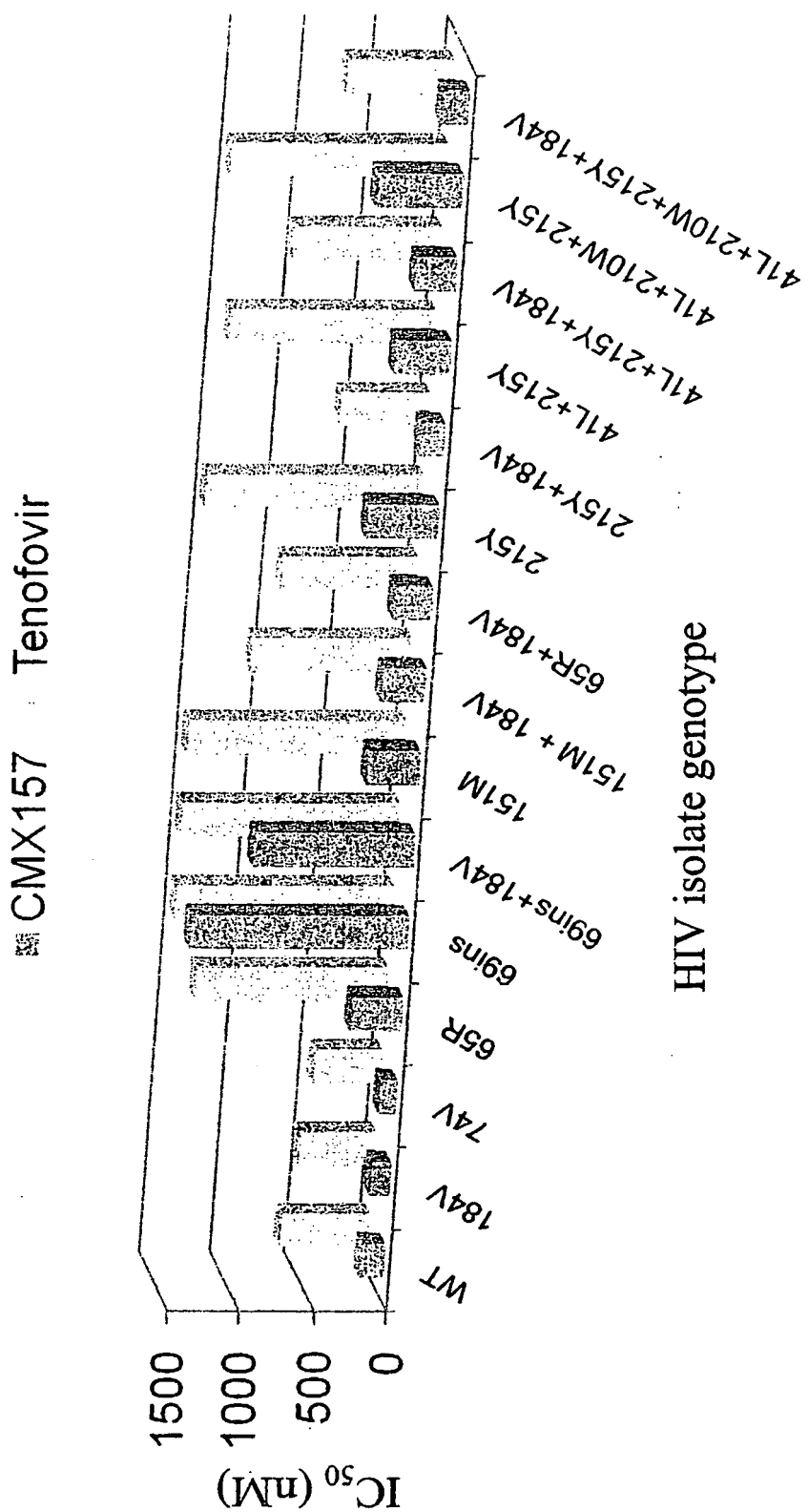


Figure 3

## REFERENCES CITED IN THE DESCRIPTION

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