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(54) Title: COMBINATIONS AND USES TREATMENTS THEREOF

(57) Abstract: Methods for treating or preventing HIV in a patient using a combination of tenofovir alafenamide (TAF) and cabotegravir are disclosed, as well as compositions containing such compounds.

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COMBINATIONS AND USES AND TREATMENTS THEREOF

FIELD OF THE INVENTION

Methods for treating or preventing HIV in a patient using a combination of: (1) tenofovir alafenamide and cabotegravir; and (2) tenofovir alafenamide, cabotegravir, and rilpivirine, are disclosed, as well as compositions comprising such compounds.

BACKGROUND OF THE INVENTION

Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor and is currently under development for the treatment and prevention of HIV. TAF has been reported to have greater antiviral activity and a lower incidence of adverse side effects when compared to tenofovir disoproxil.

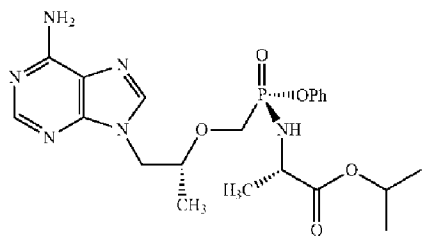
Cabotegravir is an integrase inhibitor that is currently in the clinic for the treatment of HIV infection.

Rilpivirine (TMC278) is a diarylpyrimidine (DAPY) second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) currently in clinical trials for the treatment of HIV infection and is approved and marketed in some countries under the trade name, EDURANT®, for such treatment.

Although different combinations of antiretroviral drugs have been developed for the treatment of HIV, a need still exists for alternative HIV treatment regimens.

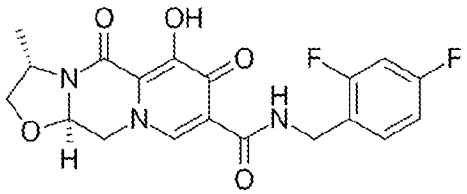
SUMMARY OF THE INVENTION

One embodiment of the invention provides a method for treating or preventing HIV in a patient comprising administering to the patient a pharmaceutically effective amount of a compound of formula I:



or a pharmaceutical composition thereof; and

an effective amount of a compound of formula II:



or a pharmaceutical composition thereof.

In another embodiment, the compound of formula I is in a pharmaceutical composition comprising the compound of formula I and fumarate.

In yet another embodiment, the compound of formula I is in a pharmaceutical composition comprising the compound of formula I and fumaric acid.

In another embodiment, the compound of formula II is in a pharmaceutical composition comprising the compound of formula II and sodium.

In another embodiment, the compound of formula I and the compound of formula II are co-administered in separate dosage forms.

In another embodiment, the compound of formula I and the compound of formula II are co-administered in a single dosage form.

In yet another embodiment, the compound of formula I and the compound of formula II are orally co-administered.

In another embodiment, the compound of formula II is in a pharmaceutical composition comprising the compound of formula II and sodium.

In a further embodiment, the compound of formula II and the compound of formula III are co-administered in a single dosage form.

In yet another embodiment, the compound of formula I and the compound of formula III are co-administered in a single dosage form.

In a further embodiment, the compound of formula II, the compound of formula II, and the compound of Formula III are co-administered in a single dosage form.

In another embodiment, the compound of formula I, the compound of formula II, and the compound of formula III are co-administered in separate dosage forms.

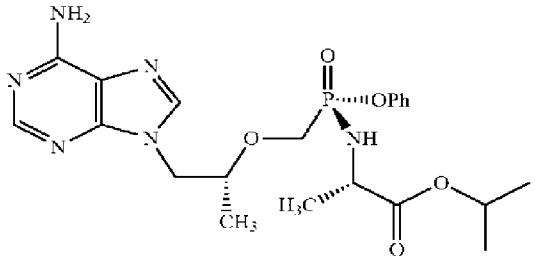
In another embodiment, the compound of formula II and the compound of formula III are co-administered in a single dosage form, and the compound of formula I is co-administered separately.

In yet another embodiment, the compound of formula II and the compound of formula III are orally co-administered.

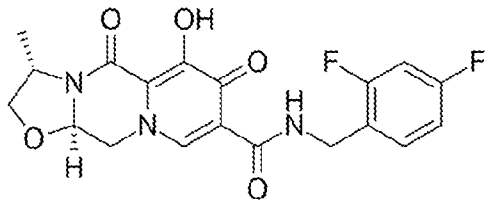
In another embodiment, the compound of formula I, the compound of formula II, and the compound of formula III are orally co-administered.

Another embodiment provides a pharmaceutically acceptable composition comprising:

a compound of formula I:

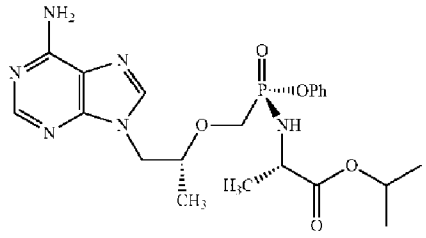


and a compound of formula II:



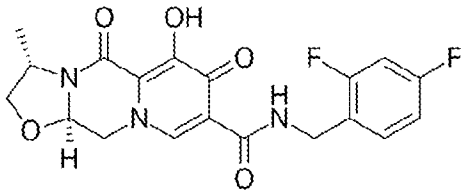
and a pharmaceutically acceptable carrier.

Yet a further embodiment of the invention provides a method for treating or preventing HIV in a patient comprising administering to the patient a pharmaceutically effective amount of a compound of formula I:



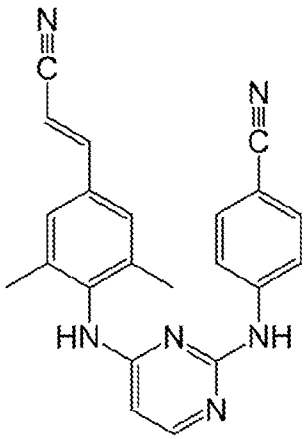
or a pharmaceutical composition thereof;

an effective amount of a compound of formula II:



or a pharmaceutical composition thereof;

and an effective amount of a compound of formula III



or a pharmaceutical composition thereof.

In another embodiment, the compound of formula III is in a pharmaceutical composition comprising the compound of formula III and hydrochloride.

In another embodiment, the compound of formula I, the compound of formula II, and the compound of formula III are co-administered in separate dosage forms.

In a further embodiment, the compound of formula I, the compound of formula II, and the compound of formula III are co-administered in separate dosage forms, wherein the compound of formula I is in an oral form, the compound of formula II is in a parenteral form, and the compound of formula III is in a parenteral form.

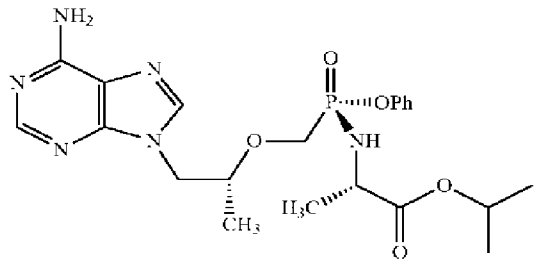
In another embodiment, the compound of formula I, the compound of formula II, and the compound of formula III are co-administered in a single dosage form.

In yet another embodiment, the compound of formula I, the compound of formula II, and the compound of formula III are co-administered.

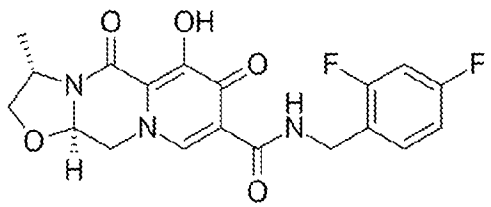
In still another embodiment, any two compounds selected from the compound of formula I, the compound of formula II, and the compound of formula III are co-administered in a single dosage form with the remaining compound in a separate dosage form.

Another embodiment provides a pharmaceutically acceptable composition comprising:

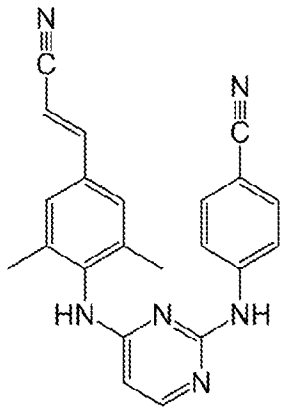
a compound of formula I:



a compound of formula II:



and a compound of formula III:



and a pharmaceutically acceptable carrier;

The combination of the compound of formula II and the compound of formula III is disclosed in U.S. 2015/0238496. Another embodiment provides further administration of at least one antiretroviral compound.

In certain embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of cabotegravir and tenofovir alafenamide, or a pharmaceutical composition thereof, in combination with a therapeutically effective amount of one or more (*e.g.*, one, two, three, one or two, or one to three) additional therapeutic agents.

In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of cabotegravir and tenofovir alafenamide, or a pharmaceutically acceptable composition thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents that are suitable for treating an HIV infection.

In one embodiment, pharmaceutical compositions comprising cabotegravir and tenofovir alafenamide, in combination with one or more (*e.g.*, one, two, three, one or two, or one to three) additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

In one embodiment, kits comprising cabotegravir and tenofovir alafenamide, or a pharmaceutical composition thereof, in combination with one or more (*e.g.*, one, two, three, one or two, or one to three) additional therapeutic agents are provided.

In certain embodiments, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, in combination with a therapeutically effective amount of one or more (*e.g.*, one, two, three, one or two, or one to three) additional therapeutic agents.

In certain embodiments, the present disclosure provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutically acceptable composition thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents that are suitable for treating an HIV infection.

In one embodiment, pharmaceutical compositions comprising cabotegravir, tenofovir alafenamide, and rilpivirine in combination with one or more (*e.g.*, one, two, three, one or two, or one to three) additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

In one embodiment, kits comprising cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, in combination with one or more (*e.g.*, one, two, three, one or two, or one to three) additional therapeutic agents are provided.In a further embodiment, kits comprising cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, in oral and/or parenteral dosage forms are provided. Certain such kits comprise tenofovir alafenamide in tablet dosage form, cabotegravir in a syringe dosage form, and rilpivirine in a syringe dosage form.

In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is chosen from: HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse tran- scriptase, HIV nucleoside or nucleotide inhibitors of reverse

transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors (*e.g.*, CCR5 inhibitors, gp41 inhibitors (*i.e.*, fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, HIV vaccines, HIV maturation inhibitors, latency reversing agents (*e.g.*, histone deacetylase inhibitors, proteasome inhibitors, protein kinase C (PKC) activators, and BRD4 inhibitors), compounds that target the HIV capsid ("capsid inhibitors"; *e.g.*, capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors, HIV p24 capsid protein inhibitors), pharmacokinetic enhancers, immune-based therapies (*e.g.*, Pd-1 modulators, Pd-Ll modulators, CTLA4 modulators, toll like receptors modulators, IL-15 agonists, HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins (*e.g.*, DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives) including those targeting HIV gp120 or gp41, combination drugs for HIV, HIV p 17 matrix protein inhibitors, IL-13 antagonists, Peptidylprolyl cis-trans isomerase A modulators, protein disulfide isomerase inhibitors, complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, integrin antagonists, nucleoprotein inhibitors, splicing factor modulators, COMM domain containing protein 1 modulators, HIV Ribo- nuclease H inhibitors, retrorocyclin modulators, CDK-9 inhibitors, dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, complement Factor H modulators, ubiquitin ligase inhibitors, deoxycytidine kinase inhibitors, cyclin dependent kinase inhibitors proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, HIV gene therapy, PI3K inhibitors, compounds, such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), WO 2013/091096Al (Boehringer Ingelheim), WO 2009/062285 (Boehringer Ingelheim), US20140221380 (Japan Tobacco), US 20140221378 (Japan Tobacco), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), W02012/003497 (Gilead Sciences), W02014/ 100323 (Gilead Sciences), W02012/145728 (Gilead Sciences), W0 2013/159064 (Gilead Sciences) and WO

2012/ 003498 (Gilead Sciences) and WO 2013/006792 (Pharma Resources), and other drugs for treating HIV, and combinations thereof.

In certain embodiments, the additional therapeutic chosen from: HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

In certain embodiments, tenofovir alafenamide and cabotegravir are formulated as a tablet that may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can contain another active ingredient for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacoki- netic enhancers, and combinations thereof. In certain embodiments, such tablets are suitable for once daily dosing.

In certain embodiments, the additional therapeutic agent may be chosen from one or more of:

(1) Combination drugs chosen from: ATRIPLA® (efavirenz+tenofovir disoproxil fumarate+emtricitabine), COMPLERA® (EVIPLERA®, rilpivirine+tenofovir disoproxil fumarate+emtricitabine), STRIBILD® (elvitegravir+cobicistat+tenofovir disoproxil fumarate+emtricitabine), lamivudine+nevirapine+zidovu dine, atazanavir sulfate+cobicistat, darunavir+cobicistat, efavirenz+lamivudine+tenofovir disoproxil fumarate, Vacc- 4x+romidepsin, APH-0812, raltegravir+lamivudine, KALE- TRA® (ALUVIA®, lopinavir+ ritonavir), atazanavir sulfate+ ritonavir, COMBIVIR® (zidovudine+lamivudine, AZT+ 3TC), EPZICOM® (Livexa®, abacavir sulfate+lamivudine, ABC+3TC), TRIZIVIR® (abacavir sulfate+zidovudine+ lamivudine, ABC+AZT+3TC), TRUVADA® (tenofovir disoproxil fumarate+emtricitabine, TDF+FTC), tenofovir+ lamivudine, atazanavir+cobicistat, doravirine+lamivudine+ tenofovir disoproxil fumarate, doravirine+lamivudine+tenofovir disoproxil and lamivudine+tenofovir disoproxil fumarate;

(2) HIV protease inhibitors chosen from: amprenavir, atazanavir, fosamprenavir, fosam- prenavir calcium, indinavir, indinavir sulfate, lopinavir, ritonavir, nelfinavir,

nelfinavir mesylate, saquinavir, saquinavir mesylate, tipranavir, brecanavir, darunavir, DG-17, TMB-657 (PPL-100), TMC-310911, and TMB-657;

(3) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase chosen from: delavirdine, delavirdine mesylate, nevirapine, (+),etravmne, dapivirine, doravirine, efavirenz, KM023, VM-1500, lentinan, AIC-292 and KM-023;

(4) HIV nucleoside or nucleotide inhibitors of reverse transcriptase chosen from: VIDEX® and VIDEX® EC (didanosine, ddl), zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, censavudine, abacavir, abacavir sulfate, amdoxovir, elvucitabine, alovudine, phosphazid, fozivudine tidoxil, apricitabine, amdoxovir, KP-1461, fosalvudine tidoxil, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, adefovir, adefovir dipivoxil, and festinavir. (5) HIV integrase inhibitors chosen from: curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phen- ethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, and TIVICAY® (dolutegravir);

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) chosen from: CX-05168, CX-05045 and CX-14442;

(7) HIV gp41 inhibitors chosen from: enfuvirtide, sifuvirtide and albuvirtide;

(8) HIV entry inhibitors, such as cenicriviroc;

(9) HIV gp120 inhibitors chosen from: Radha-108 (Receptol) and BMS-663068;

(10) CCR5 inhibitors chosen from: aplaviroc, vicriviroc, maraviroc, cenicriviroc, PR0- 140, Adaptavir (RAP-101), nifeviroc (TD-0232), TD-0680, TBR-220 (TAK-220) and vMIP (Haimipu);

(11) CD4 attachment inhibitors, such as ibalizumab;

(12) CXCR4 inhibitors chosen from: plerixafor, ALT-1188, vMIP and Haimipu;

(13) Pharmacokinetic enhancers chosen from: cobicistat and ritonavir;

(14) Immune-based therapies chosen from: dermaVir, interleukin-7, lexgenleucel-T (VRX-496), plaquenil (hydroxychloroquine), proleukin (aldesleukin, IL-2), interferon alfa, interferonalfa-2b, interferon alfa-n3, pegylated interferon alfa, interferon gamma, hydroxyurea, mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF), WF-10, ribavirin, IL-2, IL-2 XL, IL-12, polymer polyethyleneimine (PEI), Gepon, VGV-1, MOR-22, toll-like receptors modulators (tlrl, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlrlO, tlrl l, tlr12 and tlr13), BMS-936559, rintatolimod and IR-103;

(15) HIV vaccines chosen from: peptide vaccines, recombinant subunit protein vac- cines, live vector vaccines, DNA vaccines, virus-like particle vaccines (pseudovirion vaccine), CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), Remune, ITV-1, Cantre Vir,Ad5-ENVA-48, DCVax-001 (CDX-2401), PEP-6409, Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAdS), Pennvax-G, YRC-HIV MAB060-00-AB, AVX-101, Tat Oyi vaccine, AVX-201, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3NSSP ISA-51, poly-ICLC adjuvanted vaccines, Tatlmmune, GTU-multi-HIV (FIT-06), AGS-004, gp140[delta]V2.TVI+MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, Ad35-GRIN/ENV, TBC-M4, HIVAX, HIVAX-2, NYVAC-HIV-PTl, NYVAC-HIV-PT4, DNA-HIV-PT123, VIChREPOL®, rAAV1-PG9DP, GOVX-Bl l, GOVX-B21, ThV-01, TUTI-16, VGX-3300, TVI-HIV-1, Ad-4 (Ad4-env Clade C+Ad4-mGag), EN41-FPA2, PreVaxTat, TL-01, SAV-001, AE-H, MYM-VlOl, CombiHIVvac, ADVAX, MYM-V201, monomeric gp120 HIV-1 subtype C vaccine (Novartis), MVA-CMDR, MVATG-17401, ETV-01, CDX-1401, rcAd26.MOS1.HIV-Env, and DNA-Ad5 gag/pol/nef/nev (HVTN505);

(16) HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins (such as DARTs®, Duo-bodies®, Bites®, XmAbs®, TandAbs®, Fab derivatives), including BMS-936559, TMB-360 and those targeting HIV gp120 or gp41 are chosen from: bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+ C4E10, 3-BNC-117, KD-247, PGT145, PGT121, MDXOlO (ipilimumab), VRCOl, A32, 7B2, 10E8, VRC-07-523 and VRC07;

(17) latency reversing agents chosen from: histone deacetylase inhibitors such as Romidepsin, vorinostat, panobinostat; proteasome inhibitors such as VELCADE®; protein kinase C (PKC) activators such as Indolactam, prostratin, ingenol B and DAG-lactones, lono- mycin, GSK-343, PMA, SAHA, BRD4 inhibitors, IL-15, JQl, amphotericin B, and disulfram;

(18) HIV nucleocapsid p7 (NCp7) inhibitors, such as azodicarbonamide;

(19) HIV maturation inhibitors chosen from: BMS-955176 and GSK-2838232;

(20) P13K inhibitors chosen from: idelalisib, AZD-8186, buparlisib, CLR-457, pictilisib, neratinib, rigosertib, rigosertib sodium, EN-3342, TGR- 1202, alpelisib, duvelisib, UCB-5857, taselisib, XL-765, gedatolisib, VS-5584, copanlisib, CAI orotate, perifosine, RG-7666, GSK-2636771, DS-7423, panulisib, GSK- 2269557, GSK-2126458, CUDC-907, PQR-309, INCB-040093, pilaralisib, BAY-1082439, puquitinib mesylate, SAR-245409, AMG-319, RP-6530, ZSTK-474, MLN-1117, SF-1126, RV-1729, sonolisib, LY-3023414, SAR-260301 and CLR-1401;

(21) the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US20140221380 (Japan Tobacco), US20140221378 (Japan Tobacco), WO 2013/006792 (Pharma Resources), WO 2009/ 062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/091096Al (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/ 145728 (Gilead Sciences), W02012/003497 (Gilead Sciences), W02014/100323 (Gilead Sciences), W02012/ 145728 (Gilead Sciences), W02013/159064 (Gilead Sciences) and WO 2012/003498 (Gilead Sciences); and

(22) other drugs for treating HIV chosen from: REP 9, cytolin, CYT-107, alisporivir, BanLec, MK-8507, AG-1105, TR-452, MK-8591, REP 9, NOV-205, IND-02, metenkefalin, PGN-007, Acemannan, Gamimune, SCY-635, prolastin, 1,5-dicaffeoylquinic acid, BIT-225, RPI-MN, VSSP, Hlviral, IM0-3100, SB-728-T, RPI-MN, VIR-576, HGTV-43, MK-1376, rHIV7-shl-TAR-CCR5RZ, MazF gene therapy, BlockAide, ABX-464, SCY- 635, naltrexone, AAV-eCD4-Ig gene therapy, TEV-90110, TEV-90112, deferiprone, and PA-1050040 (PA-040).

In certain embodiments, cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, are combined with one, two, three, four or more additional therapeutic agents. The one, two, three, four or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

In a particular embodiment, cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof is combined with one, two, three, four or more additional therapeutic agents selected from raltegravir, Truvada® (tenofovir disoproxil fumarate+emtricitabine, TDF+FTC), maraviroc, enfuvirtide, EPZICOM® (LIVEXA®, abacavir sulfate+lamivudine, ABC+3TC), TRIZIVIR® (abacavir sulfate+zidovudine+ lamivudine, ABC+AZT+3TC), adefovir, adefovir dipivoxil, STRIBILD® (elvitegravir+cobicistat+tenofovir disoproxil fumarate+emtricitabine), raltegravir+lamivudine, COMPLERA® (EVIPLERA®, rilpivirine+tenofovir disoproxil fumarate+emtricitabine), Cobicistat, ATRIPLA® (efavirenz+tenofovir disoproxil fumarate+emtricitabine), atazanavir sulfate+cobicistat, atazanavir+cobicistat, darunavir+cobicistat, atazanavir, atazanavir sulfate, elvitegravir, ALUVIA® (KALETRA®, lopinavir+ ritonavir), ritonavir, emtricitabine, atazanavir sulfate+ ritonavir, darunavir, lamivudine, Prolastin, fosamprenavir, fosamprenavir calcium, efavirenz, COMBIVIR® (zidovudine+ lamivudine, AZT+3TC), etravirine, nelfinavir, nelfininavir mesylate, interferon, didanosine, stavudine, indinavir, indinavir sulfate, tenofovir+lamivudine, zidovudine, nevirapine, saquinavir, saquinavir mesylate, aldesleukin, zalcitabine, tipranavir, amprenavir, delavirdine, delavirdine mesylate, Radha-108 (Receptol), Rivira, lamivudine+tenofovir diso- proxil fumarate, efavirenz+lamivudine+tenofovir disoproxil fumarate, phosphazid, lamivudine+nevirapine+zidovudine, abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil and tenofovir disoproxil fumarate.

In one embodiment, tenofovir alafenamide and cabotegravir, or tenofovir alafenamide, cabotegravir, and rilpivirine, are administered with either emtricitabine or lamivudine. In certain embodiments, when cabotegravir and tenofovir alafenamide, or tenofovir alafenamide, cabotegravir, and rilpivirine, or a

pharmaceutical composition thereof is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen.. When administered sequentially, either combination may be administered in two or more administrations.

In certain embodiments, cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, rilpivirine, or a pharmaceutical composition thereof, are combined with one or more additional therapeutic agents, in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration. In certain embodiments, cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, are administered with one or more additional therapeutic agents. Co-administration of cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and one or more additional therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine or a pharmaceutical composition thereof, within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, rilpivirine, or a

pharmaceutical composition thereof, within seconds or minutes. In some embodiments, a unit dose of cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine, or a pharmaceutical composition thereof, is administered first, followed, after a period of hours (*e.g.*, 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (*e.g.*, 1-12 hours), by administration of a unit dose of cabotegravir and tenofovir alafenamide, or cabotegravir, tenofovir alafenamide, and rilpivirine or a pharmaceutical composition thereof.

In certain embodiments, cabotegravir and tenofovir alafenamide, or a pharmaceutical composition thereof, are administered orally.

In another embodiment, the combination of cabotegravir and tenofovir alafenamide is administered to the patient once a day.

In another embodiment, the combination of cabotegravir and tenofovir alafenamide is administered to the patient twice a day.

In another embodiment, cabotegravir is administered to the patient at about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg dose, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg or about 100 mg, once, twice or three times a day. In another embodiment,

cabotegravir is administered to the patient at about 25 mg to 100 mg, at about 25 mg to 75 mg, at about 35 mg to 65 mg or about 45 mg to 55 mg, once or twice per day. In another embodiment, cabotegravir is administered to the patient at about 50 mg, once or twice per day.

In a further embodiment, tenofovir alafenamide is administered to the patient at about 1 mg, about 5 mg, about 10mg, about 15mg, about 20 mg, about 25 mg dose, about 30 mg, about 35 mg, about 40 mg, about 45 mg or about 50 mg once, twice or three times a day. In another embodiment, tenofovir alafenamide is administered to

the patient at about 1 mg to 50 mg or at about 5 mg to 25 mg once per day. In another embodiment, tenofovir alafenamide is administered to the patient at about 5 mg, once per day. In another embodi- ment, tenofovir alafenamide is administered to the patient at about 10mg, once per day. In another embodiment, tenofovir alafenamide is administered to the patient at about 25 mg, once per day.

In certain embodiments, cabotegravir, tenofovir alafenamide, rilpivirine, or a pharmaceutical composition thereof, are administered orally.

In another embodiment, the combination of cabotegravir, tenofovir alafenamide, and rilpivirine is administered to the patient once a day.

In a further embodiment, the combination of cabotegravir, tenofovir alafenamide, and rilpivirine is administered to the patient twice a day.

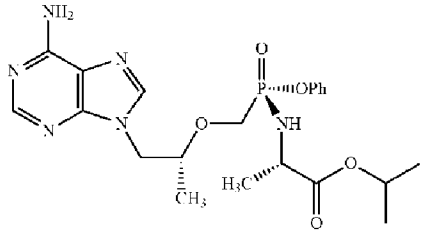
In another embodiment, rilpivirine is administered to the patient as a tablet, wherein the effective amount is: between 1 to 1000 mg of active ingredient per unit dosage form; between 5 and 200 mg of active ingredient per unit dosage form; between 1 to 1000 mg of active ingredient; or between 5 to 200 mg of active ingredient. In another embodiment, rilpivirine is administered to the patient in a tablet form at about 25 mg., once per day.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

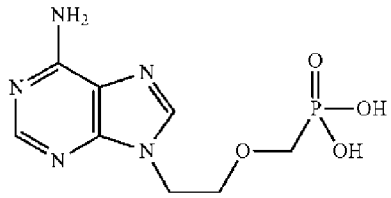
As used herein, the term "co-administer" refers to administration of two or more agents within a 24-hour period of each other, for example, as part of a clinical treatment regimen. In other embodiments, "co-administer" refers to administration of two or more agents within 2 hours of each other. In other embodiments, "co-administer" refers to administration of two or more agents within 30 minutes of each other. In other embodiments, "co-administer" refers to administration of two or more agents within 15 minutes of each other. In other embodiments, "co-administer" refers to administration at the same time, either as part of a single formulation or as multiple formulations that are administered by the same or different routes.

"Tenofovir alafenamide" or "TAF" is {9-[(R)-2- [[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxy- phosphinyl]-methoxy]propyl]adenine}:



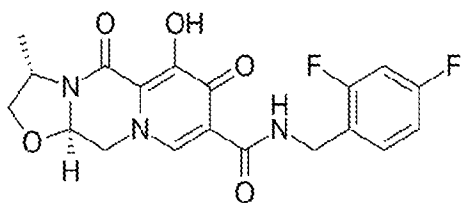
TAF may be associated with fumarate, such as monofumarate and hemifumarate. Methods for preparing TAF are disclosed in US Patent 7,390,791.

TFV or Tenofovir is:



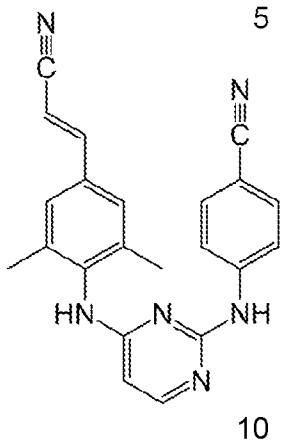
"Tenofovir disoproxil" or "TD" is 9-[(R)-2-[[bis [[(isopropoxycarbonyl)oxy]methoxy]phosphiny l]methoxy] propyl]adenine. TDF may be associated with fumarate, such as monofumarate.

"Cabotegravir" is:



Cabotegravir may be associated with sodium. Methods for preparing cabotegravir are described in US Patent 8,410,103.

"Rilpivirine is:



Rilpivirine may be associated with hydrochloride. Methods for preparing rilpivirine are described in US Patent 7,125,879.

"Emtricitabine" or "FTC" refers to (2R,5S,cis)-4- amino-5-fluoro-l-(2-hydroxymethyl-1,3-oxathiolan-5-yl)- (lH)-pyrimidin-2-one.

"Therapeutically effective amount" or "effective amount" refers to that amount of the compound being administered that will prevent a condition, or will relieve to some extent one or more of the symptoms of the disorder being treated. Pharmaceutical compositions suitable for use herein include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

As used herein, "treatment", refers to inhibition, reduction, elimination or alleviation of a disease, as well as prevention.

Combinations and Methods of Treatment

A method for the treatment or prophylaxis of diseases, disorders, and conditions is provided herein. An example of a disease, disorder, or condition includes, but is not limited to, a retrovirus infection, or a disease, disorder, or condition associated with a retrovirus infection. Retroviruses are RNA viruses and are generally classified into the alpharetrovirus, betaretrovirus, deltaretrovirus, epsilonretrovirus, gammaretrovirus, lentivirus, and spumavirus families. Examples of retroviruses include, but are not limited to, human immunodeficiency virus (HIV).

The active agents of the disclosed combination therapy may be administered to a human in any conventional manner. While it is possible for the active agents to be administered as compounds, they are preferably administered as a pharmaceutical composition that can include contact with an acid or base, either in an ionic salt form or in contact with the base or acid (*i.e.,* co-formers) without sharing ions. The salt, acid or base co-former, carrier, or diluent should be acceptable, in the sense of being compatible with the other ingredients and not deleterious to the recipient thereof. Examples of carriers or diluents for oral administration include, but are not limited to: cornstarch, lactose, magnesium stearate, talc, microcrystalline cellulose, stearic acid, povidone, crospovidone, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose (*e.g.*, low substituted hydroxypropyl cellulose), hydroxypropylmethyl cellulose (*e.g.*, hydroxypropylmethyl cellulose 2910), sodium lauryl sulfate, mannitol, sodium stearyl fumarate, and talc. Examples of salts and acid or base co-formers include fumarate, hemifumarate, sodium, and hydrochloride.

The pharmaceutical compositions may be prepared by any suitable method, such as those methods well known in the art of pharmacy, for example, methods such as those described in Gennaro, *et al.*, REMINGTON'S PHARMACEUTICAL SCIENCES (18th ed., Mack Publishing Co., 1990), especially "Part 8: Pharmaceutical Preparations and their Manufacture". Such methods include the step of bringing into association the compounds with the carrier or diluents and, optionally, one or more accessory ingredients. Such accessory ingredients include, but are not limited to: fillers, binders, excipients, disintegrants, lubricants, colorants, flavoring agents, sweeteners, preservatives (*e.g.*, antimicrobial preservatives), suspending agents, thickening agents, emulsifying agents, and/or wetting agents.

In practice, the amount of each compound to be administered ranges from about 0.001 to 100 mg per kg of body weight, such total dose being given at one time or in divided doses. Each compound will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. Alternatively, both compounds will be combined and administered as a formulation in association with one or more pharmaceutically acceptable excipients. The choice of excipient will, to a large extent, depend upon factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Such compositions and methods for their preparation may be found, for example, in REMINGTON'S PHARMACEUTICAL SCIENCES (19th Edition, Mack Publishing Company, 1995).

In the following description of the examples, specific embodiments in which the invention may be practiced are described. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and logical and other changes may be made without departing from the scope of the invention. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of the invention is defined only by the appended claims, along with the full scope of equivalents to which such claims are entitled.

Examples

Example 1: HIV Cell Line Assay The HIV cell line experiments taught by Kobayashi, *et al.*, *Antimicrobial Agents and Chemotherapy*, 55: 814-815 (2011) are followed to test the antiviral abilities of two disclosed and claimed combinations: (1) TAF plus cabotegravir; and (2) TAF plus cabotegravir plus rilpivirine as compared with the antiviral abilities of each of these three compounds alone.

Compounds. TAF, cabotegravir, and rilpivirine, are synthesized at GlaxoSmithKline®, Research Triangle Park, NC. The structures of each of these compounds are shown above in formulas I, II, and II, respectively.

Cells and viruses. Cells of MT-4, a human T-cell leukemia virus type 1 (HTLV-1)-transformed human T-cell line, are maintained as described previously [12]. 293T cells are maintained in Dulbecco's modified Eagle medium (DMEM)–F-12 medium containing 10% fetal bovine serum (FBS). Peripheral blood mononuclear cells (PBMCs) are derived from whole blood samples obtained from HIV-negative donors. PBMCs are separated from whole blood by density gradient centrifugation with Ficoll-Paque Plus® (GE Healthcare®, Waukesha, WI) according to the manufacturer's instructions and are stimulated by the addition of either 20 U/ml of interleukin-2 (IL-2) or 10% natural T-cell growth factor (ZeptoMetrix®, Buffalo, NY) plus 5 to 10 µg/ml of phytohemagglutinin (PHA). Molt-4 cells persistently infected with HIV-1 IIIB and MT-2 cells [16] are obtained from S. Harada (Kumamoto University, Kumamoto, Japan). HeLa-CD4 cells containing an HIV-1 long terminal repeat (LTR)-driven β-galactosidase reporter gene have been described previously [20]. MAGI-CCR5 cells have been described previously [9]). HIV-1 strain IIIB is derived from cell-free supernatants of cultures of the chronically infected cell line, H93B (H9/HTLV-IIIB). HIV-1 strain Ba-L is purchased from Advanced Biotechnologies Inc.® (Columbia, MD) and is expanded in PHA-activated PBMCs, while HIV-1 NL432 [1] is obtained from A. Adachi (Tokushima University, Tokushima, Japan). Plasmid pGJ3-Luci, containing a replication-defective HIV lentiviral vector expressing luciferase [21], is licensed from Christian Jassoy (University of Leipzig), and is used to create stocks of a vesicular stomatitis virus glycoprotein G (VSV-G)-pseudotyped self-inactivating pseudo-HIV (PHIV) lentiviral vector by cotransfection, along with plasmid pVSV-G (Clontech®) into CIP4 cells (a derivative of the 293T human renal epithelial cell line that expresses macrophage scavenger receptor SRA-I to improve adherence to plastic) and harvesting of the cell-free supernatant.

Antiviral assay in MT-4 cells. MT-4 cells growing exponentially at a density of

5×10^5 or 6×10^5/ml are infected with HIV-1 strain IIIB at a viral multiplicity of infection of 0.001 or a 50% tissue culture infective dose of 4 to 10. The cells are then aliquoted to 96-well plates in the presence of varying concentrations of compounds. After incubation for 4 or 5 days, antiviral activity is determined by a cell viability assay that either measures bioluminescence with a CellTiter-Glo®

luminescent reagent (Promega Corporation®, Madison, WI) or measured absorbance at 560 and 690 nm using the yellow tetrazolium MTT reagent [3-(4,5- dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide].

Pseudo-HIV assay. The antiviral activities of TAF, cabotegravir, and rilpivirine alone, as well as the combinations of: (1) TAF plus cabotegravir; and (2) TAF plus cabotegravir plus rilpivirine are measured in a single-round assay using a self-inactivating PHIV lentiviral vector. CIP4 cells (2×10^4/well) infected with an amount of PHIV sufficient to produce approximately 50,000 relative light units are added to 96-well black, clear-bottom plates and were incubated for 2 days with all three compounds at varying concentrations. Infected cells are measured as a function of luciferase activity in a luminometer using the Steady-Glo® reagent (Promega Corporation®).

Antiviral assay in PBMCs. In one 96-well culture plate, PHA- and IL-2- stimulated PBMCs (4×10^5/well) are pre-incubated with each compound alone, and then for each of the two above combinations of the compounds, for 1 h, while HIV-1 strain, Ba-L, is mixed with the same compound in a second plate. An aliquot of the Ba-L–compound mixture is then transferred to the PBMC- compound mixture and is incubated for 7 days. After this incubation, supernatants are assayed for reverse transcriptase (RT) activity by incorporation of [*methyl*-^{3}H]dTTP to measure viral replication, as previously described [15].

Effects of human serum and serum proteins. The effect of the presence of human serum albumin (HSA; 20 or 40 mg/ml), α_1-acid glycoprotein (AAG; 2 mg/ml), or human serum (HS; up to 30% or 50% is used, and results were extrapolated up to 100%) on the antiviral activity of each of TAF, cabotegravir, and rilpivirine alone is evaluated in the PHIV and MT-4 assay systems. To estimate the effects of the fold shift in protein binding, antiviral activity is tested with the addition of various concentrations of human serum to the HIV-1 IIIB replication assay mixture in MT-4 cells, as previously described [15]. The protein-adjusted half-maximal effective concentration (PA-EC_{50}) is estimated by multiplying the EC_{50} in PBMCs by the fold shift value. The same experiment is conducted using the combinations of: (1) TAF plus cabotegravir; (2) TAF plus cabotegravir plus rilpivirine.

Combination antiviral activity assay in MT-4 cells. The *in vitro* combination activity relationships of: (1) cabotegravir alone; (2) TAF alone; (3) rilpivirine alone; (4) cabotegravir plus TAF; and (5) cabotegravir plus TAF plus rilpivirine are determined as previously described [39]. Multiple concentrations of the compounds are tested in checkerboard dilution fashion in the presence and absence of dilutions of approved anti-HIV drugs, adefovir, or ribavirin. The assay used HIV-1 IIIB-infected MT-4 cells, and the interaction of compound combinations is analyzed by dose wise additivity-based calculations to quantify deviation from dose wise additivity at the 50% level. Wells containing the top concentration of compounds by themselves are compared to wells with the top concentration of each of the two compound combinations in order to show that combination effects are due to the drugs used, and not simply to toxicity. Assays with the MT-4 system format are run as described previously [15]. Fractional inhibitory concentration (FIC) values in the range of 0.1 to 0.2 indicate weak synergy; values that approach 0.5 indicate strong synergy; and positive values of 0.1 to 0.2 indicate weak antagonism. The effects of the anti-hepatitis B virus (anti-HBV) and anti-HCV agents adefovir and ribavirin on: (1) cabotegravir alone; (2) TAF alone; (3) rilpivirine alone; (4) TAF plus cabotegravir; and (5) TAF plus cabotegravir plus rilpivirine are examined using linear regression, as described previously [41]. Because the HIV-1 IIIB MT-4 system is CXCR4-based, the CCR5 inhibitor, maraviroc, is evaluated in a checker-board dilution format using MAGI-CCR5 cells with the Gal Screen reagent (Tropix®, Bedford, MA) for chemiluminescent endpoints, and data are analyzed as described by Prichard and Shipman [37] by using the MacSynergy II® program. Synergy volumes in the range of -50 to 50 define additivity; <-50, antagonism; and >50, synergy.

The results of these experiments are expected to show that the combinations of both: (1) cabotegravir plus TAF; and (2) cabotegravir plus TAF plus rilpivirine are synergistic in their antiviral abilities as compared to the antiviral abilities of each compound alone. Specifically, in each of the HIV cell-based assays described above, both these combinations are expected to be synergistic in each combination's ability to inhibit HIV replication in cells over that expected with each of the three compounds alone.

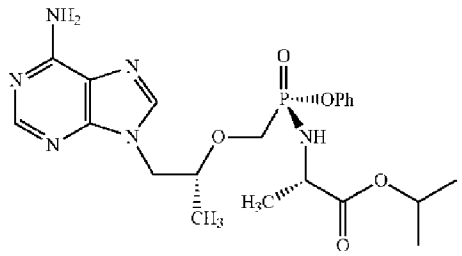
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9. Chackerian, *et al.*, *J. Virol.* 71:3932–3939 (1997).
12. Daluge, *et al.*, *Antimicrob. Agents Chemother.* 38:1590–1603. (1994).
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21. Jármy, *et al.*, *J. Med. Virol.* 64:223–231 (2001).
37. Prichard, et al., *Antiviral Res.* 14:181–205 (1990).
39. Selleseth, *et al.*, *Antimicrob. Agents Chemother.* 47:1468–1471 (2003).
41. Tukey, *et al.*, *Biometrics* 41:295–301 (1985).

[1] The reference numbering used in this example is the same as that used in Kobayashi, *et al.*, *supra*.

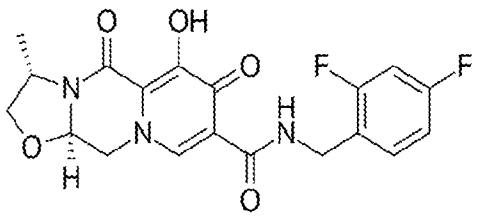
We claim:

1. A method for treating or preventing human immunodeficiency virus (HIV) in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount of a compound of Formula I:



or a pharmaceutical composition thereof; and

an effective amount of a compound of Formula II:



or a pharmaceutical composition thereof.

2. The method as claimed in Claim 1, wherein the compound of formula I is in a pharmaceutical composition comprising fumaric acid and the compound of formula I.

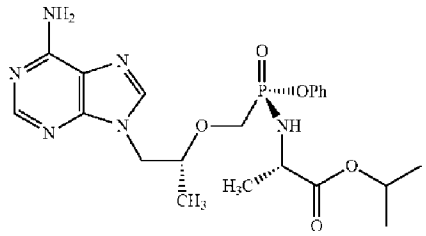
3. The method of as claimed in Claim 1, wherein the compound of formula II is in a pharmaceutical composition comprising the compound of formula II and sodium.

4. The method as claimed in Claim 1, wherein the compound of formula I and the compound of formula II are co-administered in separate dosage forms.

5. The method as claimed in Claim 1, wherein the compound of formula I and the compound of formula II are co-administered in a single dosage form.

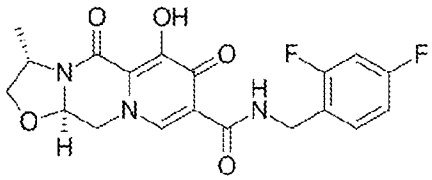
6. The method as claimed in Claim 1, wherein the method further comprises administering emtricitabine.

7. A pharmaceutically acceptable composition comprising:



or a pharmaceutical composition thereof; and

an effective amount of a compound of Formula II:



and at least one pharmaceutically acceptable carrier.

8. The pharmaceutically acceptable composition as claimed in Claim 7, wherein the compound of formula I is in contact with fumaric acid, and the compound of formula II is in contact with sodium.

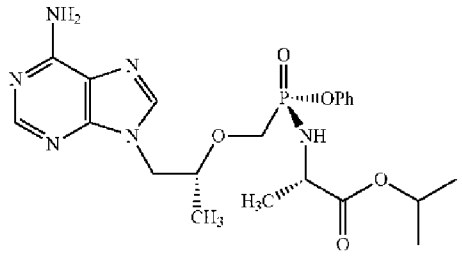
9. The pharmaceutically acceptable composition as claimed in Claim 7, said composition, further comprising emtricitabine.

10. A kit comprising:

(1) a composition comprising tenofovir alafenamide and emtricitabine;

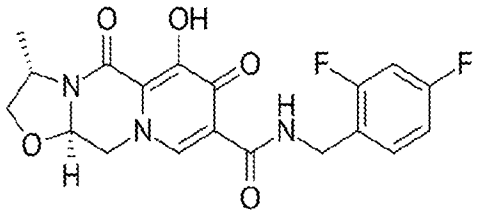
(2) a composition comprising cabotegravir; and instructions for their co-administration.

11. A method for treating or preventing human immunodeficiency virus (HIV) in a patient in need thereof, comprising administering to the patient an effective amount of a com- pound of Formula I:



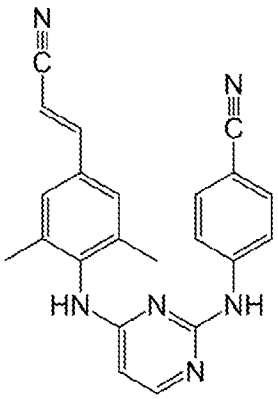
or a pharmaceutical composition thereof;

an effective amount of a compound of Formula II:



or a pharmaceutical composition thereof;

and an effective amount of a compound of Formula III:



or a pharmaceutical composition thereof.

12. The method as claimed in Claim 11, wherein the compound of formula I is in a pharmaceutical composition comprising fumaric acid, and the compound of formula II is in a pharmaceutical composition comprising sodium.

13. The method of as claimed in Claim 11, wherein the compound of formula I is in a pharmaceutical composition comprising fumaric acid, the compound of formula II is in a pharmaceutical composition comprising sodium, and the compound of formula III is in a pharmaceutical composition comprising hydrochloride.

14. The method as claimed in Claim 11, wherein the compound of formula I, the

compound of formula II, and the compound of formula III are co-administered in separate dosage forms.

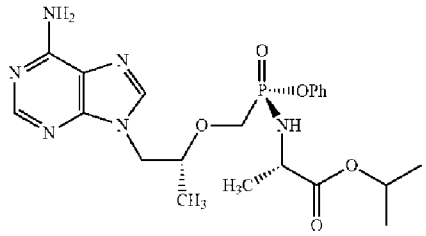
15. The method as claimed in Claim 11, wherein the compound of formula II and the compound of formula III are co-administered in a single dosage form.

16. The method as claimed in Claim 11, wherein the method further comprises administering emtricitabine.

17. The method as claimed in Claim 11, wherein the compound of formula II and the compound of formula III are co-administered in a single dosage form.

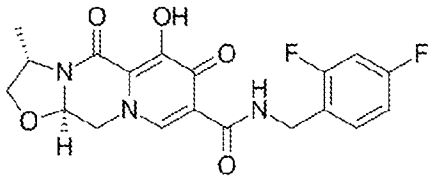
18. The method as claimed in Claim 11, wherein the method further comprises administering emtricitabine.

19. A pharmaceutically acceptable composition comprising:

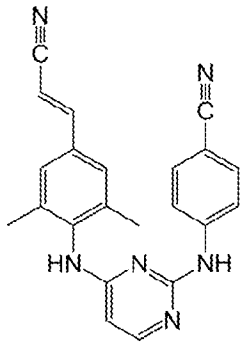


or a pharmaceutical composition thereof; and

an effective amount of a compound of Formula II:



and an effective amount of a compound of Formula III:



and at least one pharmaceutically acceptable carrier.

20. A kit comprising:

(1) a composition comprising tenofovir alafenamide and emtricitabine;

(2) composition comprising cabotegravir;

(3) a composition comprising rilpivirine; and instructions for their co-administration.

21. The composition as claimed in Claim 19, wherein the compound of formula I is in contact with fumaric acid, the compound of formula II is in contact with sodium, and the compound of formula III is in contact with hydrochloride.

22. The composition as claimed in Claim 19, wherein the compound of formula I, the compound of formula II, and the compound of formula III are co-administered in separate dosage forms.

23. The method as claimed in Claim 19, wherein the compound of formula II and the compound of formula III are co-administered in a single dosage form.

24. The method as claimed in Claim 19, wherein the method further comprises administering emtricitabine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/34404

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/20, B82Y 5/00 (2017.01)
CPC - A61K 9/0048, A61K 9/08, A61K 31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/067255 A1 (Gilead Sciences, Inc.) 10 March 2016 (10.03.2016); para [0006], [0013]-[0014], [0024], [0057], [0059]-[0061], [0074], [0078], claim 21	1-24
A	WO 2011/119566 A1 (GLAXOSMITHKLINE LLC) 29 September 2011 (29.09.2011); pg. 1, para 2	1-24
A	US 2015/238496 A1 (ViiV Healthcare Company) 27 August 2015 (27.08.2015); entire document	1-24
A	Highleyman "Cabotegravir and rilpivirine effective for HIV maintenance therapy at 96 weeks" Nam aidsmap. 19 March 2015 (19.03.2015) <http://www.aidsmap.com/Cabotegravir-and-rilpivirine-effective-for-HIV-maintenance-therapy-at-96-weeks/page/2954476/>; entire document	1-24
A	ClinicalTrials.gov "View of NCT02720094 on 2016_03_24" 24 March 2016 (24.03.2016) <https://clinicaltrials.gov/archive/NCT02720094/2016_03_24>; entire document	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2017	25 AUG 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774