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(54) Title: COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

(57) Abstract: The use of the hemifumarate form of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} (tenofovir alafenamide hemifumarate) in combination with cobicistat is disclosed. In addition, the combination of tenofovir alafenamide hemifumarate, cobicistat, emtricitabine, and elvitegravir, and the combination of tenofovir alafenamide hemifumarate, cobicistat, emtricitabine, and darunavir, are disclosed.

TITLE

COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Patent Application No. 61/594,894, filed February 3, 2012; U.S. Provisional Patent Application No. 61/618,411, filed March 30, 2012; U.S. Provisional Patent Application No. 61/624,676, filed April 16, 2012; U.S. Provisional Patent Application No. 61/692,392, filed August 23, 2012; and U.S. Provisional Patent Application No. 61/737,493, filed December 14, 2012, the content of each of which is hereby incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

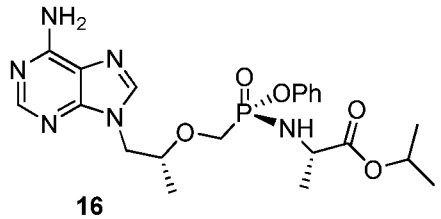
Field of the Invention

[0002] Tenofovir {9-R-[(2-phosphonomethoxy)propyl]adenine}, an acyclic nucleotide analog of dAMP, is a potent *in vitro* and *in vivo* inhibitor of human immunodeficiency virus type 1 (HIV-1) replication. Tenofovir is sequentially phosphorylated in the cell by AMP kinase and nucleoside diphosphate kinase to the active species, tenofovir diphosphate, which acts as a competitive inhibitor of HIV-1 reverse transcriptase that terminates the growing viral DNA chain. The presence of a nonhydrolyzable phosphonic acid moiety in tenofovir circumvents an

initial phosphorylation step that can be rate limiting for the activation of nucleoside analog inhibitors of HIV reverse transcriptase. Due to the presence of a phosphonate group, tenofovir is negatively charged at neutral pH, thus limiting its oral bioavailability.

[0003] Tenofovir disoproxil fumarate (TDF; VIREAD®), the first generation oral prodrug of tenofovir, has been extensively studied in clinical trials and has received marketing authorization in many countries as a once-daily tablet (300 mg) in combination with other antiretroviral agents for the treatment of HIV-1 infection.

[0004] U.S. Patent No. 7,390,791 describes certain prodrugs of phosphonate nucleotide analogs that are useful in therapy. One such prodrug is 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]-methoxy]propyl]adenine **16**:



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[0005] GS-7340 {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} is an isopropylalaninyl phenyl ester prodrug of tenofovir (9-[(2-phosphonomethoxy) propyl]adenine). GS-7340 exhibits potent anti-HIV activity 500- to 1000-fold enhanced activity relative to tenofovir against HIV-1 in T cells, activated peripheral blood mononuclear lymphocytes (PBMCs), and macrophages. GS-7340 also has enhanced ability to deliver and increase the accumulation of the parent tenofovir into PBMCs and other lymphatic tissues *in vivo*. It is also a potent inhibitor of hepatitis B virus.

[0006] GS-7340 is metabolized to tenofovir, which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, tenofovir diphosphate (PMPApp). The cellular enzymes responsible for tenofovir metabolism to the active diphosphorylated form are

adenylate kinase and nucleotide diphosphate kinase, which are highly active and ubiquitous. Adenylate kinase exists as multiple isozymes (AK1 to AK4), with the phosphorylation of tenofovir mediated most efficiently by AK2.

[0007] Tenofovir does not interact significantly with human drug metabolizing cytochrome P450 enzymes or UDP-glucuronosyltransferases as a substrate, inhibitor, or inducer, *in vitro* or *in vivo* in humans. GS-7340 has limited potential to alter cytochrome P450 enzyme activity through inhibition (IC_{50} > 7μM compared to all isoforms tested). Similarly GS-7340 does not inhibit UGT1A1 function at concentrations up to 50 μM. In addition, GS-7340 is not an activator of either the aryl hydrocarbon receptor or human pregnane X receptor.

[0008] Although tenofovir and GS-7340 show desirable activities, the treatment cost and the potential for unwanted side effects can both increase as the required dose of a drug increases. Therefore, there is a need for methods and compositions that are useful for achieving an acceptable anti-viral effect using a reduced dose of tenofovir or GS-7340.

[0009] Along with U.S. Patent No. 7,390,791, U.S. Patent No. 7,803,788 (the content of each of which is incorporated by reference herein in its entirety) also describes certain prodrugs of phosphonate nucleotide analogs that are useful in therapy. As noted above, one such prodrug is 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. This compound is also known by the Chemical Abstract name L-alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester. U.S. Patent Nos. 7,390,791 and 7,803,788 disclose a monofumarate form of this compound and its preparation method (see, e.g., Example 4).

SUMMARY OF THE INVENTION

[0010] It has been determined that the systemic exposure to GS-7340 in humans improves when GS-7340 is administered with cobicistat (1,3-thiazol-5-ylmethyl (2R,5R)-(5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-

2-yl)carbamate). When administered with cobicistat, GS-7340 was calculated to have a systemic exposure equivalent 2.2 fold higher than a dose of GS-7340 alone. In another case, GS-7340 administered with cobicistat was calculated to have a systemic exposure equivalent 3-4 fold higher than a dose of GS-7340 alone. In another case, GS-7340 administered with cobicistat was calculated to have a systemic exposure equivalent 1.3 fold higher than a dose of GS-7340 alone.

[0011] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. The cobicistat may be coadministered with GS-7340. GS-7340 or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg, or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and cobicistat or a pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount of GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount of cobicistat or pharmaceutically acceptable salt thereof, may be used. The virus of the viral infection may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0012] In one embodiment, the invention provides for the use of the compound GS-7340, or a pharmaceutically acceptable salt thereof, and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the pharmacokinetics of GS-7340. The cobicistat may be coadministered with GS-7340. GS-7340, or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg, or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount cobicistat or pharmaceutically acceptable salt thereof may be used. The

use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0013] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the C_{max} of GS-7340. The cobicistat may be coadministered with GS-7340. GS-7340 or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount of GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount of cobicistat or pharmaceutically acceptable salt thereof may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0014] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for improving blood levels of GS-7340. The cobicistat may be coadministered with GS-7340. GS-7340 or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. GS-7340, or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount GS-7340 or a pharmaceutically acceptable salt thereof, and a daily amount cobicistat or pharmaceutically acceptable salt thereof may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0015] In one embodiment, the invention provides for a composition comprising a unit-dosage form of GS-7340 or a pharmaceutically acceptable salt thereof; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent. The composition may include GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The composition may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The unit dosage form may be a single daily dosage.

[0016] In one embodiment, the invention provides for a kit comprising: (1) GS-7340, or a pharmaceutically acceptable salt thereof; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the GS-7340 or a pharmaceutically acceptable salt thereof with the cobicistat or the pharmaceutically acceptable salt thereof. The kit may include GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The kit may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg.

[0017] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering GS-7340 with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the GS-7340 provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat. GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with GS-7340. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0018] In one embodiment, the invention provides for a method for inhibiting activity of a retroviral reverse transcriptase in a human comprising coadministering GS-7340 with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the GS-7340 provides a systemic exposure

of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat. GS-7340 or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with GS-7340. The virus may be human immunodeficiency virus (HIV).

[0019] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection. The invention further provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection in a human. GS-7340 or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount (or, in some embodiments throughout, in a therapeutic amount). GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0020] In one embodiment, the invention provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. The invention further provides for the use of the compound GS-7340 or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human. GS-7340 or a

pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV).

[0021] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of GS-7340, or a pharmaceutically acceptable salt thereof, following administration to a human. GS-7340 or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0022] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof, following administration to a human. GS-7340 or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof, may be used in amounts of 3 mg,

8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth herein. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0023] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of GS-7340 by about 30-70%, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0024] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of GS-7340 by about 2-4 fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of GS-7340 by about 3 fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0025] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering 1) GS-7340 or a pharmaceutically acceptable salt thereof; and 2) cobicistat, or a pharmaceutically acceptable salt thereof to the human. GS-7340 or a pharmaceutically acceptable salt thereof is administered in a subtherapeutic amount. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0026] In one embodiment, the invention provides for a use of a subtherapeutic dose of GS-7340 coadministered with cobicistat for treating a viral infection. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0027] In one embodiment, the invention provides for the use of a subtherapeutic dose of GS-7340 coadministered with cobicistat for inhibiting retroviral reverse transcriptase. The virus may be human immunodeficiency virus (HIV).

[0028] In one embodiment, the invention provides for an anti-virus agent(s) comprising (a) a compound GS-7340 or a pharmaceutically acceptable salt thereof and (b) cobicistat, or a pharmaceutically acceptable salt thereof. The anti-virus agent(s) may include GS-7340 or a pharmaceutically acceptable salt thereof may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The anti-virus agent(s) may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of GS-7340 comparable to the systemic exposure obtainable by administration of a greater dose of GS-7340 in the absence of cobicistat is used in the manufacture of the medicament. The anti-virus agent may further include 200 mg of emtricitabine and 150 mg of elvitegravir. The anti-virus agent may further include 150 mg cobicistat, 8 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 25or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 8 mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 10 mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine.

[0029] In one embodiment, the invention provides for a unit-dosage of GS-7340 or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, wherein the unit-dosage is a daily dose. GS-7340 may be present in a subtherapeutic amount. The unit-dosage may further include 150 mg cobicistat, 8 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may further include 150 mg cobicistat, 25or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may further

include 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may include 150 mg cobicistat, 10 mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine.

[0030] In one embodiment, the invention provides the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof, following administration to a human. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be, e.g., human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0031] In one embodiment, the invention provides cobicistat for use in improving the pharmacokinetics of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof, following administration to a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0032] In one embodiment, the invention provides a kit comprising: (1) {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof with the cobicistat or a pharmaceutically acceptable salt thereof.

[0033] In one embodiment, the invention provides a kit comprising: (1) a unit dosage form comprising 5-100 mg of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine}, or a pharmaceutically acceptable salt thereof; (2) a unit dosage form comprising 150 mg cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more

containers; and (4) prescribing information regarding administering the {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof with cobicistat or a pharmaceutically acceptable salt thereof.

[0034] In one embodiment, the invention provides a use of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or its pharmaceutically acceptable salt for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human, comprising administering GS-7340 or a pharmaceutically acceptable salt thereof, and cobicistat, or a pharmaceutically acceptable salt thereof to the human. The virus may be human immunodeficiency virus (HIV).

[0035] In one embodiment, the invention provides {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or its pharmaceutically acceptable salt; and cobicistat, or a pharmaceutically acceptable salt thereof; for use in inhibiting activity of a retroviral reverse transcriptase in a human.

[0036] In one embodiment, the invention provides a use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament for a human useful for reducing a dose between about 30-70% of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0037] In one embodiment, the invention provides the use of {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof; and cobicistat or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of a viral infection in a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0038] In one embodiment, the invention provides an anti-viral agent(s) comprising (a) {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} or a pharmaceutically acceptable salt thereof, which is used in combination with (b) cobicistat or a pharmaceutically acceptable salt thereof for use in the prophylactic or therapeutic treatment of a viral infection in a human.

[0039] It has also been determined that the systemic exposure to tenofovir in humans improves when tenofovir is administered with cobicistat. When administered with cobicistat, tenofovir was calculated to have a systemic exposure equivalent 3 to 4 fold higher than a dose of tenofovir alone.

[0040] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. Tenofovir may be used in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg. The tenofovir or a pharmaceutically acceptable salt thereof, and the cobicistat or pharmaceutically acceptable salt thereof may be coadministered. The use may provide a unit dosage form comprising a daily amount tenofovir or a pharmaceutically acceptable salt thereof, and a daily amount cobicistat or pharmaceutically acceptable salt thereof is administered. The virus may be human immunodeficiency virus (HIV).

[0041] In one embodiment, the invention provides for a composition comprising a unit-dosage form of tenofovir or a pharmaceutically acceptable salt thereof; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent. Tenofovir may be present in the composition in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg.

[0042] In one embodiment, the invention provides for a kit that includes (1) tenofovir, or a pharmaceutically acceptable salt thereof; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir or a

pharmaceutically acceptable salt thereof with the cobicistat or the pharmaceutically acceptable salt thereof. Tenofovir may be present in the kit in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg.

[0043] In one embodiment, the invention provides for a method of treating a viral infection in a human that includes coadministering tenofovir with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the tenofovir provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. Tenofovir may be administered in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be administered in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0044] In one embodiment, the invention provides for a method for inhibiting activity of a retroviral reverse transcriptase in a human comprising coadministering tenofovir with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of tenofovir coadministered with the cobicistat provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. Tenofovir may be coadministered in amounts of less than 300 mg, 200 mg or less and 100 mg or less. Cobicistat may be coadministered in amounts of 50-500 mg, 100-400 mg, 100-300 mg, and 150 mg. The virus may be human immunodeficiency virus (HIV)

[0045] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0046] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with

cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection in a human. The tenofovir or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount (or, in some embodiments throughout, in a therapeutic amount). Tenofovir may be administered in amounts of less than 300 mg, 200 mg or less and 100 mg or less. The cobicistat may be administered in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat is used in the manufacture of the medicament. Cobicistat in an amount of 150 mg may be used in the manufacture of the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0047] In one embodiment, the invention provides for the use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0048] In one embodiment, the invention provides for use of the compound tenofovir or a pharmaceutically acceptable salt thereof coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human. The tenofovir or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. Tenofovir may be used in amounts of less than 300 mg, 200 mg or less and 100 mg or less. The cobicistat may be coadministered in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat is used in the manufacture of the medicament. Cobicistat in an amount of 150 mg may be coadministered. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0049] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of tenofovir, or a pharmaceutically acceptable salt thereof, following administration to a human. The tenofovir or a pharmaceutically acceptable salt thereof may be used in a subtherapeutic amount. Tenofovir or a pharmaceutically acceptable salt thereof, may be coadministered to the human in an amount of 100 mg or less, 200 mg or less or in amount less than 300 mg. Cobicistat may be used in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat is used in the manufacture of the medicament. Cobicistat in an amount 150 mg may be used to prepare the medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0050] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir by about 30-70%, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0051] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir by about 2 to 4 fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir by about 3-fold, or a pharmaceutically acceptable salt thereof, upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0052] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering 1) tenofovir or a pharmaceutically acceptable salt thereof; and 2) cobicistat, or a pharmaceutically acceptable salt thereof to the human. The tenofovir or a pharmaceutically acceptable salt thereof may be administered in a subtherapeutic amount. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0053] In one embodiment, the invention provides for a use of a subtherapeutic dose of tenofovir coadministered with cobicistat for treating a viral infection. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0054] In one embodiment, the invention provides for a use of a subtherapeutic dose of tenofovir coadministered with cobicistat for inhibiting retroviral reverse transcriptase. The virus may be human immunodeficiency virus (HIV).

[0055] In one embodiment, the invention provides for an anti-virus agent(s) comprising (a) a compound tenofovir or a pharmaceutically acceptable salt thereof and (b) cobicistat, or a pharmaceutically acceptable salt thereof. The tenofovir may be present in the anti-virus agent(s) in a subtherapeutic amount. The tenofovir may be present in the anti-virus agent(s) in an amount of 100 mg or less, 200 mg or less or less than 300 mg. The cobicistat coadministered with the tenofovir may be present in the anti-virus agent(s) in an amount that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. The anti-virus agent may further include cobicistat in an amount of 150 mg. The anti-virus agent may further include 200 mg of emtricitabine and 150 mg of elvitegravir. The anti-virus agent may include 150 mg cobicistat, 100 or less mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 200 or less mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, less than 300 mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 50 mg tenofovir, 150 mg elvitegravir, and 200 mg emtricitabine. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0056] In one embodiment, the invention provides for a unit-dosage of tenofovir or a pharmaceutically acceptable salt thereof and cobicistat, or a pharmaceutically acceptable salt thereof, wherein the unit-dosage is a daily dose. Tenofovir may be present in a subtherapeutic amount. The unit-dosage may include 100 mg or less, 200 mg or less or less than 300 mg of tenofovir. The unit-dosage may include an amount of cobicistat that provides a systemic exposure of tenofovir comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir in the absence of cobicistat. The unit-dosage may include 150 mg of cobicistat. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0057] Also described is a hemifumarate form of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The name for 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine (GS-7340) is tenofovir alafenamide. The hemifumarate form of tenofovir alafenamide is also referred to herein as tenofovir alafenamide hemifumarate.

[0058] In one embodiment of the invention is provided tenofovir alafenamide hemifumarate, especially in combination with cobicistat and/or with other an additional therapeutic agent or agents.

[0059] In another embodiment is provided tenofovir alafenamide hemifumarate, wherein the ratio of fumaric acid to tenofovir alafenamide is 0.5 ± 0.1, or 0.5 ± 0.05, or 0.5 ± 0.01, or about 0.5.

[0060] In one embodiment is provided tenofovir alafenamide hemifumarate in a solid form.

[0061] In one embodiment is provided tenofovir alafenamide hemifumarate that has an X-ray powder diffraction (XRPD) pattern having 2theta values of 6.9 ± 0.2° and 8.6 ± 0.2°. In another embodiment is provided tenofovir alafenamide hemifumarate wherein the XRPD pattern comprises 2theta values of 6.9 ± 0.2°, 8.6 ± 0.2°, 11.0 ± 0.2°, 15.9 ± 0.2°, and 20.2 ± 0.2°.

[0062] In one embodiment is provided tenofovir alafenamide hemifumarate that has a differential scanning calorimetry (DSC) onset endotherm of 131 ± 2 °C, or 131 ± 1 °C.

[0063] In one embodiment is provided a pharmaceutical composition comprising tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient. In another embodiment is provided the pharmaceutical composition, further comprising an additional therapeutic agent. In a further embodiment, the additional therapeutic agent is selected from the group consisting of human immunodeficiency virus (HIV) protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, CCR5 inhibitors, and additional protease inhibiting compounds.

[0064] In one embodiment is provided a method for treating a human immunodeficiency virus (HIV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HIV infection comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising tenofovir alafenamide hemifumarate. In a further embodiment, the method comprises administering to the subject one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, CCR5 inhibitors, and additional protease inhibiting compounds.

[0065] In one embodiment is provided a method for treating a hepatitis B virus (HBV) infection comprising administering to a subject in need thereof a therapeutically effective amount of tenofovir alafenamide hemifumarate. In another embodiment is provided a method for treating an HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition comprising tenofovir alafenamide hemifumarate.

[0066] In one embodiment is provided a method for preparing a pharmaceutical composition comprising combining tenofovir alafenamide hemifumarate and a pharmaceutically acceptable excipient to provide the pharmaceutical composition.

[0067] In one embodiment is provided tenofovir alafenamide hemifumarate for use in medical therapy.

[0068] In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HIV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HIV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HIV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HIV infection.

[0069] In one embodiment is provided the use of tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of an HBV infection. In another embodiment is provided the use of tenofovir alafenamide hemifumarate to treat an HBV infection. In a further embodiment is provided the use of tenofovir alafenamide hemifumarate for the preparation or manufacture of a medicament for the treatment of an HBV infection. In another further embodiment is provided tenofovir alafenamide hemifumarate for use in treating an HBV infection.

[0070] In some embodiments of the invention, the methods of treating and the like comprise administration of multiple daily doses. In other embodiments, the methods of treating and the like comprise administration of a single daily dose.

[0071] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. The cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat or pharmaceutically acceptable salt thereof may be coadministered. A unit dosage form comprising a daily amount of tenofovir alafenamide hemifumarate, and a daily amount of cobicistat or

pharmaceutically acceptable salt thereof may be used. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0072] In one embodiment, the invention provides for the use tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the pharmacokinetics of tenofovir alafenamide hemifumarate. Cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat, or pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount of tenofovir alafenamide hemifumarate, and a daily amount of cobicistat or pharmaceutically acceptable salt thereof may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0073] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for improving the C_{max} of tenofovir alafenamide hemifumarate. The cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat or a pharmaceutically acceptable salt thereof may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat, or pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount of tenofovir alafenamide hemifumarate, and a daily amount of cobicistat, or a pharmaceutically acceptable salt thereof, may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0074] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt

thereof, for improving blood levels of tenofovir alafenamide hemifumarate. The cobicistat may be coadministered with tenofovir alafenamide hemifumarate. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat, or a pharmaceutically acceptable salt thereof, may be used in an amount of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, may be coadministered. A unit dosage form comprising a daily amount tenofovir alafenamide hemifumarate, and a daily amount cobicistat, or a pharmaceutically acceptable salt thereof, may be used. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0075] In one embodiment, the invention provides for a composition comprising a unit-dosage form of tenofovir alafenamide hemifumarate; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent. The composition may include tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The composition may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The unit-dosage form may be a single daily dosage.

[0076] In one embodiment, the invention provides for a kit comprising: (1) tenofovir alafenamide hemifumarate; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir alafenamide hemifumarate with the cobicistat, or the pharmaceutically acceptable salt thereof. The kit may include tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The kit may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg.

[0077] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering tenofovir alafenamide hemifumarate with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the tenofovir alafenamide

hemifumarate provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat. Tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with tenofovir alafenamide hemifumarate. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0078] In one embodiment, the invention provides for a method for inhibiting activity of a retroviral reverse transcriptase in a human comprising coadministering tenofovir alafenamide hemifumarate with cobicistat, or a pharmaceutically acceptable salt thereof, wherein the dose of cobicistat coadministered with the tenofovir alafenamide hemifumarate provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat. Tenofovir alafenamide hemifumarate or a pharmaceutically acceptable salt thereof in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below may be coadministered with cobicistat. Cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg may be coadministered with tenofovir alafenamide hemifumarate. The virus may be human immunodeficiency virus (HIV).

[0079] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection. The invention further provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a viral infection in a human. Tenofovir alafenamide hemifumarate may be used in a subtherapeutic amount (or, in some embodiments throughout, in a therapeutic amount). Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat

may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0080] In one embodiment, the invention provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. The invention further provides for the use of tenofovir alafenamide hemifumarate coadministered with cobicistat, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human. Tenofovir alafenamide hemifumarate may be used in a subtherapeutic amount. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the medicament. The virus may be human immunodeficiency virus (HIV).

[0081] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of tenofovir alafenamide hemifumarate following administration to a human. Tenofovir alafenamide hemifumarate may be used in a subtherapeutic amount. Tenofovir alafenamide hemifumarate may be used in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. Cobicistat may be used in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. Cobicistat may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the

medicament. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0082] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir alafenamide hemifumarate by about 30-70% upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0083] In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir alafenamide hemifumarate by about 2-4 fold upon administration of the cobicistat. In one embodiment, the invention provides for the use of cobicistat, or a pharmaceutically acceptable salt thereof; to prepare a medicament for a human useful for reducing a dose of tenofovir alafenamide hemifumarate by about 3 fold upon administration of the cobicistat. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0084] In one embodiment, the invention provides for a method of treating a viral infection in a human comprising coadministering 1) tenofovir alafenamide hemifumarate; and 2) cobicistat, or a pharmaceutically acceptable salt thereof, to the human. Tenofovir alafenamide hemifumarate is administered in a subtherapeutic amount. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0085] In one embodiment, the invention provides for a use of a subtherapeutic dose of tenofovir alafenamide hemifumarate coadministered with cobicistat for treating a viral infection. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0086] In one embodiment, the invention provides for the use of a subtherapeutic dose of tenofovir alafenamide hemifumarate coadministered with cobicistat for

inhibiting retroviral reverse transcriptase. The virus may be human immunodeficiency virus (HIV)

[0087] In one embodiment, the invention provides for an anti-virus agent(s) comprising (a) tenofovir alafenamide hemifumarate and (b) cobicistat, or a pharmaceutically acceptable salt thereof. The anti-virus agent(s) may include tenofovir alafenamide hemifumarate in amounts of 3 mg, 8 ± 3 mg, 10 ± 5 mg, 25 ± 5 mg, or 40 ± 10 mg or other ranges as set forth below. The anti-virus agent(s) may include cobicistat in amounts of 50-500 mg, 100-400 mg, 100-300 mg or 150 mg. The cobicistat may be used in an amount that provides a systemic exposure of tenofovir alafenamide hemifumarate comparable to the systemic exposure obtainable by administration of a greater dose of tenofovir alafenamide hemifumarate in the absence of cobicistat in the manufacture of the medicament. The anti-virus agent may further include 200 mg of emtricitabine and 150 mg of elvitegravir. The anti-virus agent may further include 150 mg cobicistat, 8 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 25 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may further include 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 8 mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The anti-virus agent may include 150 mg cobicistat, 10 mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine.

[0088] In one embodiment, the invention provides for a unit-dosage of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, wherein the unit-dosage is a daily dose. Tenofovir alafenamide hemifumarate may be present in a subtherapeutic amount. The unit-dosage may further include 150 mg cobicistat, 8 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may further include 150 mg cobicistat, 25or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage

may further include 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine. The unit-dosage may include 150 mg cobicistat, 10 mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine.

[0089] In one embodiment, the invention provides the use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for improving the pharmacokinetics of tenofovir alafenamide hemifumarate following administration to a human. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0090] In one embodiment, the invention provides cobicistat for use in improving the pharmacokinetics of tenofovir alafenamide hemifumarate following administration to a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0091] In one embodiment, the invention provides a kit comprising: (1) tenofovir alafenamide hemifumarate; (2) cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir alafenamide hemifumarate with the cobicistat or a pharmaceutically acceptable salt thereof.

[0092] In one embodiment, the invention provides a kit comprising: (1) a unit dosage form comprising 5-100 mg of tenofovir alafenamide hemifumarate; (2) a unit dosage form comprising 150 mg cobicistat, or a pharmaceutically acceptable salt thereof; (3) one or more containers; and (4) prescribing information regarding administering the tenofovir alafenamide hemifumarate with cobicistat or a pharmaceutically acceptable salt thereof.

[0093] In one embodiment, the invention provides a use of tenofovir alafenamide hemifumarate for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase in a human, comprising administering tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, to the human. The virus may be human immunodeficiency virus (HIV).

[0094] In one embodiment, the invention provides tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for use in inhibiting activity of a retroviral reverse transcriptase in a human.

[0095] In one embodiment, the invention provides a use of cobicistat, or a pharmaceutically acceptable salt thereof, to prepare a medicament for a human useful for reducing a dose between about 30-70% of tenofovir alafenamide hemifumarate upon administration of the cobicistat. The medicament may be used for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0096] In one embodiment, the invention provides the use of tenofovir alafenamide hemifumarate and cobicistat, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. The use may be for the prophylactic or therapeutic treatment of a viral infection in a human. The virus may be human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0097] In one embodiment, the invention provides an anti-viral agent(s) comprising (a) tenofovir alafenamide hemifumarate, which is used in combination with (b) cobicistat, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment of a viral infection in a human.

[0098] In one embodiment, the invention provides for the use of ritonavir in the compositions, kits, unit-dosages and uses set forth above in place of cobicistat.

[0099] In one embodiment, the invention provides a method for inhibiting Pgp-mediated intestinal secretion of GS-7340, or a pharmaceutically acceptable salt thereof, in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, with GS-7340, or a pharmaceutically acceptable salt thereof. In one embodiment, 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 10 mg of GS-7340, or a pharmaceutically acceptable salt thereof.

[0100] In one embodiment, the invention provides a method for inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, with tenofovir alafenamide hemifumarate. In one embodiment, 150 mg of

cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 10 mg of tenofovir alafenamide hemifumarate.

[0101] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine.

[0102] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine to the human.

[0103] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg GS-7340, 150 mg elvitegravir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0104] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine.

[0105] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine to the human.

[0106] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 150 mg elvitegravir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0107] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) tenofovir alafenamide hemifumarate, (b) cobicistat, or a pharmaceutically acceptable salt thereof, (c) emtricitabine, and (d) darunavir.

[0108] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 8 or less mg of tenofovir alafenamide hemifumarate, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0109] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 25 or less mg of tenofovir alafenamide hemifumarate, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0110] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 10 mg of tenofovir alafenamide hemifumarate, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0111] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) GS-7340, or a pharmaceutically acceptable salt thereof, (b) cobicistat, or a pharmaceutically acceptable salt thereof, (c) emtricitabine, and (d) darunavir.

[0112] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 8 or less mg of GS-7340, or a pharmaceutically acceptable salt thereof, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0113] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 25 or less mg of GS-7340, or a pharmaceutically acceptable salt thereof, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0114] In one embodiment, the invention provides an anti-virus agent(s) comprising (a) 10 mg of GS-7340, or a pharmaceutically acceptable salt thereof, (b) 150 mg of cobicistat, or a pharmaceutically acceptable salt thereof, (c) 200 mg of emtricitabine, and (d) 800 mg of darunavir.

[0115] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg GS-7340, 800 mg of darunavir, and 200 mg emtricitabine.

[0116] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg GS-7340, 800 mg of darunavir, and 200 mg emtricitabine to the human.

[0117] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg GS-7340, 800 mg of darunavir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0118] In one embodiment, the invention provides the use of an anti-virus agent for the prophylactic or therapeutic treatment of a viral infection in a human, wherein the anti-virus agent comprises 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 800 mg of darunavir, and 200 mg emtricitabine.

[0119] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 800 mg of darunavir, and 200 mg emtricitabine to the human.

[0120] In one embodiment, the invention provides the use of 150 mg cobicistat, 10 or less mg tenofovir alafenamide hemifumarate, 800 mg of darunavir, and 200 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0121] In one embodiment, the invention provides the use of a dose of a cytochrome p450 inhibitor, or a pharmaceutically acceptable salt thereof, to boost a dose GS-7340, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a viral infection in a human. In one embodiment, the cytochrome p450 inhibitor is cobicistat, or a pharmaceutically acceptable salt thereof. In one further embodiment, the dose of GS-7340 would be a subtherapeutic amount absent the dose of cobicistat.

[0122] In one embodiment, the invention provides a composition comprising: a unit-dosage form of GS-7340, or a pharmaceutically acceptable salt thereof; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent, wherein the amount of GS-7340 in the unit-dosage form is a subtherapeutic amount.

[0123] In one embodiment, the invention provides the use of a dose of a cytochrome p450 inhibitor, or a pharmaceutically acceptable salt thereof, to boost a dose tenofovir alafenamide hemifumarate for the prophylactic or therapeutic treatment of a viral infection in a human. In one embodiment, the cytochrome p450 inhibitor is cobicistat, or a pharmaceutically acceptable salt thereof. In one

further embodiment, the dose of tenofovir alafenamide hemifumarate would be a subtherapeutic amount absent the dose of cobicistat.

[0124] In one embodiment, the invention provides a composition comprising: a unit-dosage form of tenofovir alafenamide hemifumarate; a unit-dosage form of cobicistat, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent, wherein the amount of tenofovir alafenamide hemifumarate in the unit-dosage form is a subtherapeutic amount.

[0125] In one embodiment, the invention provides the uses and methods related to treating a viral infection, as noted herein, wherein the viral infection is human immunodeficiency virus (HIV).

[0126] In one embodiment, the invention provides the uses and methods related to treating a viral infection, as noted herein, wherein the viral infection is Hepatitis B virus (HBV).

[0127] In one embodiment, the invention provides a method of treating a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein the composition contains an amount of cobicistat, or a pharmaceutically acceptable salt thereof, sufficient for an amount of tenofovir alafenamide hemifumarate in the composition to provide an effect on the viral infection that is greater than the effect of the amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0128] In one embodiment, the invention provides a method of treating a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein an effect on the viral infection of an amount of tenofovir alafenamide hemifumarate in the composition is greater than the effect of the same amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0129] In one embodiment, the invention provides an anti-viral treatment method on a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein the composition contains an amount of cobicistat, or a pharmaceutically acceptable salt thereof, sufficient for an amount of tenofovir alafenamide hemifumarate in the composition to provide an anti-viral effect that is greater than the anti-viral effect of the amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0130] In one embodiment, the invention provides an anti-viral treatment method on a viral infection in a human, comprising administering to the human a composition comprising cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, wherein an anti-viral effect of an amount of tenofovir alafenamide hemifumarate in the composition is greater than the anti-viral effect of the same amount of tenofovir alafenamide hemifumarate in the absence of cobicistat, or a pharmaceutically acceptable salt thereof, and wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0131] In one embodiment, the invention provides a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate. In a further embodiment, the composition comprises: 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof; and 3-40 mg of tenofovir alafenamide hemifumarate. In another embodiment, the composition further comprises a pharmaceutically acceptable carrier or diluent.

[0132] In one embodiment, the invention provides a method of treating a viral infection in a human comprising administering a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate, to the human.

[0133] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, to the human.

[0134] In one embodiment, the invention provides a method of inhibiting activity of a retroviral reverse transcriptase comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate. In a further embodiment, the coadministering of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, is in a human.

[0135] In one embodiment, the invention provides use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0136] In one embodiment, the invention provides use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for treating a viral infection in a human.

[0137] In one embodiment, the invention provides use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase. In a further embodiment, the medicament is for inhibiting activity of a retroviral reverse transcriptase in a human.

[0138] In one embodiment, the invention provides a method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising administering a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate, to the human.

[0139] In one embodiment, the invention provides a method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate to the human. In a further embodiment, 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

[0140] In one embodiment, the invention provides a method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human comprising administering a composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate, to the human.

[0141] In one embodiment, the invention provides a method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate. In a further embodiment, 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

[0142] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0143] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir. In a further embodiment, the composition comprises: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0144] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir to the human. In a further embodiment, the method comprises coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir to the human.

[0145] In one embodiment, the invention provides use of a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0146] In one embodiment, the invention provides use of (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention

provides use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the manufacture of a medicament for treating a viral infection in a human.

[0147] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0148] In one embodiment, the invention provides a composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0149] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0150] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir. In a further embodiment, the composition comprises: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0151] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir to the human. In a further embodiment, the method comprises coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir to the human.

[0152] In one embodiment, the invention provides use of a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0153] In one embodiment, the invention provides use of (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir for the manufacture of a medicament for treating a viral infection in a human.

[0154] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) darunavir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0155] In one embodiment, the invention provides a composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 400-1600 mg darunavir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0156] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0157] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and emtricitabine. In a further embodiment, the composition comprises: 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0158] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering tenofovir alafenamide hemifumarate and emtricitabine to the human. In a further embodiment, the method comprises coadministering 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine to the human.

[0159] In one embodiment, the invention provides use of a composition comprising: tenofovir alafenamide hemifumarate and emtricitabine for the prophylactic or therapeutic treatment of a viral infection in a human.

[0160] In one embodiment, the invention provides use of tenofovir alafenamide hemifumarate and emtricitabine for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0161] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0162] In one embodiment, the invention provides a composition comprising: 3-40 mg tenofovir alafenamide hemifumarate and 50-500 mg emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0163] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0164] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine. In a further embodiment, the composition comprises: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine. In a further embodiment, the invention provides a method of treating a viral infection in a human comprising administering such a composition to the human.

[0165] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine to the human. In a further embodiment, the method comprises coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine to the human.

[0166] In one embodiment, the invention provides use of a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine, for the prophylactic or therapeutic treatment of a viral infection in a human.

[0167] In one embodiment, the invention provides use of (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine for the manufacture of a medicament for treating a viral infection in a human.

[0168] In one embodiment, the invention provides a composition comprising: (a) tenofovir alafenamide hemifumarate; (b) rilpivirine; and (c) emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0169] In one embodiment, the invention provides a composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 10-80 mg rilpivirine; and (c) 50-500 mg emtricitabine for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0170] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0171] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and GS-9441. In a further embodiment, the composition comprises: 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441. In a further embodiment, the invention provides a method of

treating a viral infection in a human comprising administering such a composition to the human.

[0172] In one embodiment, the invention provides a method of treating a viral infection in a human comprising coadministering tenofovir alafenamide hemifumarate and GS-9441 to the human. In a further embodiment, the method comprises coadministering 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441 to the human.

[0173] In one embodiment, the invention provides use of a composition comprising: tenofovir alafenamide hemifumarate and GS-9441 for the prophylactic or therapeutic treatment of a viral infection in a human.

[0174] In one embodiment, the invention provides use of tenofovir alafenamide hemifumarate and GS-9441 for the manufacture of a medicament for treating a viral infection in a human. In a further embodiment, the invention provides use of 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441 for the manufacture of a medicament for treating a viral infection in a human.

[0175] In one embodiment, the invention provides a composition comprising: tenofovir alafenamide hemifumarate and GS-9441 for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0176] In one embodiment, the invention provides a composition comprising: 3-40 mg tenofovir alafenamide hemifumarate and 5-1500 mg GS-9441 for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

[0177] In additional embodiments, the invention provides the methods and uses disclosed wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

BRIEF DESCRIPTION OF THE DRAWINGS

[0178] Figure 1 shows pharmacokinetic data from patients dosed with various doses of GS-7340 and TDF.

[0179] Figure 2 shows pharmacokinetic data from patients dosed with various doses of GS-7340 and TDF.

[0180] Figure 3A-B shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0181] Figure 4A-B shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0182] Figure 5A-B shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0183] Figure 6 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0184] Figure 7 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0185] Figure 8 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0186] Figure 9 shows pharmacokinetic data from patients dosed with various formulations of GS-7340.

[0187] Figure 10A-B shows results of substrate assays in cells transfected with the genes for human P-glycoprotein (Pgp; MDR1) and breast cancer resistance protein (BCRP) genes.

[0188] Figure 11A-B shows results of bidirectional permeability assays in cells transfected with the genes for human Pgp and BCRP.

[0189] Figure 12A-F shows results of bidirectional permeability assays in cells transfected with the genes for human Pgp and BCRP.

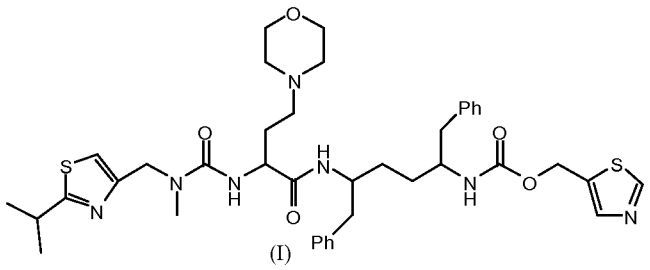
[0190] Figure 13 shows the X-ray powder diffraction (XRPD) pattern of tenofovir alafenamide hemifumarate.

[0191] Figure 14 shows a graph of the DSC analysis of tenofovir alafenamide hemifumarate.

[0192] Figure 15 shows a graph of the thermogravimetric analysis (TGA) data for tenofovir alafenamide hemifumarate.

[0193] Figure 16 shows a graph of the dynamic vapor sorption (DVS) analysis of tenofovir alafenamide hemifumarate.

DETAILED DESCRIPTION OF THE INVENTION

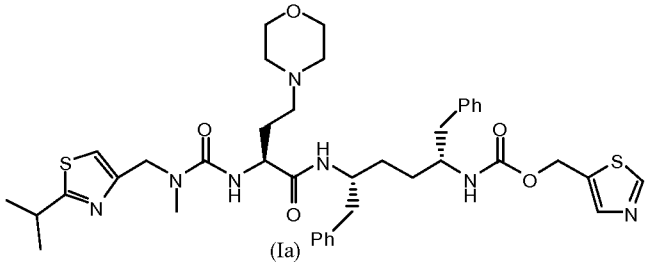


(I)

[0194] Cobicistat (chemical name 1,3-thiazol-5-ylmethyl (2R,5R)-(5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-2-yl)carbamate) is a chemical entity that has been shown to be a mechanism-based inhibitor that irreversibly inhibits CYP3A enzymes.

[0195] Detailed enzyme inactivation kinetic studies were performed comparing cobicistat with ritonavir. Cobicistat was found to be an efficient inactivator of human hepatic microsomal CYP3A activity with kinetic parameters similar to those of ritonavir. In addition, cobicistat is a moderate inhibitor of CYP2B6 (similar potency to ritonavir), a weak inhibitor of CYP2D6, and does not appreciably inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, or uridine glucuronosyltransferase 1A1. In xenobiotic receptor transactivation and human hepatocyte studies, cobicistat displayed no/weak potential as an inducer of cytochrome P450, UGT1A1, or P-glycoprotein (at up to 30 μM). Permeability assays suggest that cobicistat is not a strong substrate or inhibitor of transporters including P-glycoprotein, MRP1, and MRP2. Inhibition of intestinal P-glycoprotein by cobicistat is only possible during absorption due to its high aqueous solubility, but it is not potent enough to inhibit transporters at systemic concentrations. These data indicate that, compared to ritonavir, cobicistat is a more selective inhibitor of CYP3A *in vitro* and a weaker inducer of CYP enzymes, which may potentially result in fewer clinically significant interactions with substrates of other CYP enzymes.

[0196] Cobicistat may also be present in compositions enriched with a stereoisomer of formula (Ia):



(Ia)

which is thiazol-5-ylmethyl (2R,5R)-5-((S)-2-(3-((2-isopropylthiazol-5-yl)methyl)-3-methylureido)-4-morpholinobutanamido)-1,6-diphenylhexan-2-ylcarbamate.

[0197] In one embodiment, the cobicistat has an enriched concentration of 85 ± 5% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat has an enriched concentration of 90 ± 5% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat has an enriched concentration of 95 ± 2% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat has an enriched concentration of 99 ± 1% of the stereoisomer of formula (Ia). In another embodiment, the cobicistat is present as the pure stereoisomer of formula (Ia).

[0198] Coadministration of cobicistat with GS-7340 or tenofovir alafenamide hemifumarate boosts systemic exposure to GS-7340 or tenofovir alafenamide hemifumarate in humans, improves the pharmacokinetics of GS-7340 or tenofovir alafenamide hemifumarate (including, but not limited to, C_{max} increases), and increases blood levels of GS-7340 / tenofovir alafenamide hemifumarate / tenofovir. Therefore, GS-7340 or tenofovir alafenamide hemifumarate coadministered with cobicistat may be administered in lower amounts than previously thought to achieve a therapeutic effect. Such lower amounts may be amounts that would be subtherapeutic in the absence of coadministration of cobicistat.

[0199] Without being bound by any theory of the invention, it is believed that cobicistat may be acting to inhibit intestinal Pgp-mediated intestinal secretion of GS-7340 or tenofovir alafenamide hemifumarate. In *in vitro* studies, cobicistat and ritonavir significantly increased the accumulation of probe substrates (such as

calcein AM and Hoechst 33342) in cells transfected with P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP), and cobicistat was found to be a substrate for these transporters. Cobicistat appears to be a substrate of Pgp and BCRP and likely has a competitive mode of inhibition with coadministered agents. Cobicistat appears to be a relatively weak inhibitor of Pgp and BCRP and may only have a transient effect on these transporters during intestinal absorption, facilitated by high solubility of, and resulting high concentrations of, cobicistat achievable in the gastrointestinal tract. Combined, these results suggest that cobicistat can effectively inhibit intestinal transporters and increase the absorption of coadministered substrates, including HIV protease inhibitors and GS-7340 or tenofovir alafenamide hemifumarate, contributing to its effectiveness as a pharmacoenhancer.

[0200] As used herein, the term "coadminister" (or "coadministration") 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, "coadminister" refers to administration of two or more agents within 2 hours of each other. In other embodiments, "coadminister" refers to administration of two or more agents within 30 minutes of each other. In other embodiments, "coadminister" refers to administration of two or more agents within 15 minutes of each other. In other embodiments, "coadminister" refers to administration of two or more agents at the same time, either as part of a single formulation or as multiple formulations that are administered by the same or different routes.

[0201] The term "unit dosage form" refers to a physically discrete unit, such as a capsule, tablet, or solution, that is suitable as a unitary dosage for a human patient, each unit containing a predetermined quantity of one or more active ingredient(s) calculated to produce a therapeutic effect, in association with at least one pharmaceutically acceptable diluent or carrier, or combination thereof. Unit dosage formulations contain a daily dose or unit daily subdose or an appropriate fraction thereof, of the active ingredient(s).

[0202] The term "subtherapeutic amount" of a compound is any amount of the compound that upon dosing is insufficient to achieve the desired therapeutic benefit.

[0203] The term "boosting amount" or "boosting dose" is the amount of a compound needed to improve the pharmacokinetics of a second compound (or increase availability or exposure). The boosting amount or boosting dose may improve the pharmacokinetics (or increase availability or exposure) of the second compound to a level that is therapeutic in a subject. In other words, a subtherapeutic amount of the second compound (i.e., subtherapeutic when administered without coadministration of the boosting amount) reaches a therapeutic level(s) in a subject due to improved pharmacokinetics (or increased availability or exposure) upon coadministration of the boosting amount.

[0204] The present invention also provides a method for the treatment or prophylaxis of diseases, disorders, and conditions. 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), human T-lymphotropic virus (HTLV), rous sarcoma virus (RSV), and the avian leukosis virus. In general, three genes of the retrovirus genome code for the proteins of the mature virus: *gag* (group-specific antigen) gene, which codes for the core and structural proteins of the virus; *pol* (polymerase) gene, which codes for the enzymes of the virus, including reverse transcriptase, protease, and integrase; and *env* (envelope) gene, which codes for the retrovirus surface proteins.

[0205] Retroviruses attach to and invade a host cell by releasing a complex of RNA and the *pol* products, among other things, into the host cell. The reverse transcriptase then produces double-stranded DNA from the viral RNA. The double-stranded DNA is imported into the nucleus of the host cell and integrated into the host cell genome by the viral integrase. A nascent virus from the integrated DNA is formed when the integrated viral DNA is converted into mRNA by the host cell polymerase, and the proteins necessary for virus formation are produced by the action of the virus protease. The virus particle undergoes budding and is released from the host cell to form a mature virus.

[0206] The active agents may be administered to a human in any conventional manner. While it is possible for the active agents to be administered as raw compounds, they are preferably administered as a pharmaceutical composition. The salt, 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 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), and sodium lauryl sulfate.

[0207] 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 GS-7340 or tenofovir alafenamide hemifumarate with the carrier or diluent and optionally one or more accessory ingredients. Such accessory ingredients include those conventional in the art, such as, fillers, binders, excipients, disintegrants, lubricants, colorants, flavoring agents, sweeteners, preservatives (e.g., antimicrobial preservatives), suspending agents, thickening agents, emulsifying agents, and/or wetting agents.

[0208] The term "GS-7340, or pharmaceutically acceptable salt thereof" or the like includes any amorphous, crystalline, co-crystalline, complex, or other physical form thereof. In one embodiment, a composition comprising a pharmaceutically acceptable coformer and GS-7340 is administered. The pharmaceutically acceptable coformer can be any pharmaceutically acceptable compound that is capable of forming a "pharmaceutically acceptable salt" with GS-7340. For example, the pharmaceutically acceptable coformer can be a pharmaceutically acceptable acid (e.g. adipic acid, L-aspartic acid, citric acid, fumaric acid, maleic acid, malic acid, malonic acid, succinic acid, tartaric acid, or oxalic acid). In one embodiment of the invention, the pharmaceutically acceptable coformer is a bis-acid. In another embodiment, the pharmaceutically acceptable coformer is

fumaric acid. In another embodiment, a composition comprising a coformer and GS-7340 in a ratio of about 0.5 ± 0.05 can be administered. One form of GS-7340 is a hemifumarate form (tenofovir alafenamide hemifumarate), as described further herein.

[0209] The pharmaceutical compositions may provide controlled, slow release or sustained release of the agents (e.g., GS-7340 or tenofovir alafenamide hemifumarate) over a period of time. The controlled, slow release or sustained release of the agents (e.g., GS-7340 or tenofovir alafenamide hemifumarate) may maintain the agents in the bloodstream of the human for a longer period of time than with conventional formulations. Pharmaceutical compositions include, but are not limited to, coated tablets, pellets, solutions, powders, capsules, and dispersions of GS-7340 or tenofovir alafenamide hemifumarate in a medium that is insoluble in physiologic fluids, or where the release of the therapeutic compound follows degradation of the pharmaceutical composition due to mechanical, chemical, or enzymatic activity.

[0210] The pharmaceutical compositions of the invention may be, for example, in the form of a pill, capsule, solution, powder, or tablet, each containing a predetermined amount of GS-7340 or tenofovir alafenamide hemifumarate. In an embodiment of the invention, the pharmaceutical composition is in the form of a tablet comprising GS-7340 or tenofovir alafenamide hemifumarate. In another embodiment of the invention, the pharmaceutical composition is in the form of a tablet comprising GS-7340 and the components of the tablet utilized and described in the Examples provided herein.

[0211] For oral administration, fine powders or granules may contain diluting, dispersing, and or surface active agents and may be present, for example, in water or in a syrup, in capsules or sachets in the dry state, or in a nonaqueous solution or suspension wherein suspending agents may be included, or in tablets wherein binders and lubricants may be included.

[0212] When administered in the form of a liquid solution or suspension, the formulation may contain GS-7340 or tenofovir alafenamide hemifumarate and purified water. Optional components in the liquid solution or suspension include suitable sweeteners, flavoring agents, preservatives (e.g., antimicrobial

preservatives), buffering agents, solvents, and mixtures thereof. A component of the formulation may serve more than one function. For example, a suitable buffering agent also may act as a flavoring agent as well as a sweetener.

[0213] Suitable sweeteners include, for example, saccharin sodium, sucrose, and mannitol. A mixture of two or more sweeteners may be used. The sweetener or mixtures thereof are typically present in an amount of from about 0.001% to about 70% by weight of the total composition. Suitable flavoring agents may be present in the pharmaceutical composition to provide a cherry flavor, cotton candy flavor, or other suitable flavor to make the pharmaceutical composition easier for a human to ingest. The flavoring agent or mixtures thereof are typically present in an amount of about 0.0001% to about 5% by weight of the total composition.

[0214] Suitable preservatives include, for example, methylparaben, propylparaben, sodium benzoate, and benzalkonium chloride. A mixture of two or more preservatives may be used. The preservative or mixtures thereof are typically present in an amount of about 0.0001% to about 2% by weight of the total composition.

[0215] Suitable buffering agents include, for example, citric acid, sodium citrate, phosphoric acid, potassium phosphate, and various other acids and salts. A mixture of two or more buffering agents may be used. The buffering agent or mixtures thereof are typically present in an amount of about 0.001% to about 4% by weight of the total composition.

[0216] Suitable solvents for a liquid solution or suspension include, for example, sorbitol, glycerin, propylene glycol, and water. A mixture of two or more solvents may be used. The solvent or solvent system is typically present in an amount of about 1% to about 90% by weight of the total composition.

[0217] The pharmaceutical composition may be coadministered with adjuvants. For example, nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecyl polyethylene ether may be administered with or incorporated into the pharmaceutical composition to artificially increase the permeability of the intestinal walls. Enzymatic inhibitors may also be administered with or incorporated into the pharmaceutical composition.

GS-7340

[0218] In one embodiment of the invention, a dose of 3 mg, 3 ± 2 mg, or 3 ± 1 mg of GS-7340, or a pharmaceutically acceptable salt thereof, is administered.

[0219] In one embodiment of the invention, a dose of 8 ± 3 mg, 8 ± 2 mg or 8 ± 1 mg of GS-7340, or a pharmaceutically acceptable salt thereof, is administered.

[0220] In one embodiment of the invention, a unit dosage form comprises a dose of 8 ± 2 mg of GS-7340, or a pharmaceutically acceptable salt thereof.

[0221] In various embodiments of the invention, a dose of 8 ± 3 mg; 25 ± 10 mg; 10 ± 5 mg; 25 ± 5 mg; 25 ± 2 mg; 40 ± 10 mg; 40 ± 5 mg; 40 ± 2 mg; 60 ± 20 mg; 60 ± 10 mg; 100 ± 20 mg; 100 ± 10 mg; 125 ± 20 mg; 125 ± 10 mg; 150 ± 20 mg; 150 ± 10 mg; 200 ± 40 mg; or 200 ± 15 mg of GS-7340, or a pharmaceutically acceptable salt thereof, is administered.

[0222] The desired daily dose of GS-7340 also may be administered as two, three, four, five, six, or more subdoses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0223] The concentration of tenofovir / GS-7340 in the bloodstream may be measured as the plasma concentration (e.g., ng/mL). Pharmacokinetic parameters for determining the plasma concentration include, but are not limited to, the maximum observed plasma concentration (C_{max}), observed plasma concentration at the end of the dosing interval or "trough" concentration (C_{tau} or C_{min}), area under the plasma concentration time curve (AUC) from time zero up to the last quantifiable time point ($AUC_{0\text{-}last}$), AUC from time zero to infinity ($AUC_{0\text{-}inf}$), AUC over the dosing interval (AUC_{tau}), time of maximum observed plasma concentration after administration (t_{max}), and half-life of GS-7340 in plasma ($t_{1/2}$).

[0224] Administration of GS-7340 with food according to the methods of the invention may also increase absorption of GS-7340. Absorption of GS-7340 may be measured by the concentration attained in the bloodstream over time after administration of GS-7340. An increase in absorption by administration of GS-7340 with food may also be evidenced by an increase in C_{max} and/or AUC of GS-7340 as compared to the values if GS-7340 was administered without food. Typically protease inhibitors are administered with food.

Tenofovir alafenamide hemifumarate

[0225] In one embodiment, there is provided a hemifumarate form of tenofovir alafenamide (i.e., tenofovir alafenamide hemifumarate). This form may have a ratio (i.e., a stoichiometric ratio or mole ratio) of fumaric acid to tenofovir alafenamide of 0.5 ± 0.1, 0.5 ± 0.05, 0.5 ± 0.01, or about 0.5, or the like.

[0226] In one embodiment, tenofovir alafenamide hemifumarate consists of fumaric acid and tenofovir alafenamide in a ratio of 0.5 ± 0.1.

[0227] In one embodiment, tenofovir alafenamide hemifumarate consists essentially of fumaric acid and tenofovir alafenamide in a ratio of 0.5 ± 0.1.

[0228] In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising 2theta values of 6.9 ± 0.2°, 8.6 ± 0.2°, 10.0 ± 0.2°, 11.0 ± 0.2°, 12.2 ± 0.2°, 15.9 ± 0.2°, 16.3 ± 0.2°, 20.2 ± 0.2°, and 20.8 ± 0.2°.

[0229] In one embodiment, tenofovir alafenamide hemifumarate has an XRPD pattern comprising at least four 2theta values selected from 6.9 ± 0.2°, 8.6 ± 0.2°, 10.0 ± 0.2°, 11.0 ± 0.2°, 12.2 ± 0.2°, 15.9 ± 0.2°, 16.3 ± 0.2°, 20.2 ± 0.2°, and 20.8 ± 0.2°.

[0230] In one embodiment, tenofovir alafenamide hemifumarate has a DSC onset endotherm of 131 ± 2 °C, or 131 ± 1 °C.

[0231] In various embodiments, a tenofovir alafenamide hemifumarate composition comprises less than about 5%; 1%; or 0.5% by weight of tenofovir alafenamide monofumarate.

[0232] In one embodiment, a tenofovir alafenamide hemifumarate composition comprises no detectable tenofovir alafenamide monofumarate.

[0233] Tenofovir alafenamide (i.e., the compound 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine) can be prepared as described in U.S. Patent No. 7,390,791.

[0234] In various embodiments of the invention, a dose of 3 mg; 3 ± 2 mg; 3 ± 1 mg; 8 ± 3 mg; 8 ± 2 mg; 8 ± 1 mg;

[0235] In one embodiment of the invention, a unit dosage form comprises a dose of 8 ± 2 mg of tenofovir alafenamide hemifumarate.

[0236] 25 ± 10 mg; 10 ± 5 mg; 10 mg; 25 ± 5 mg; 25 ± 2 mg; 40 ± 10 mg; 40 ± 5 mg; 40 ± 2 mg; 60 ± 20 mg; 60 ± 10 mg; 100 ± 20 mg; 100 ± 10 mg;

125 ± 20 mg; 125 ± 10 mg; 150 ± 20 mg; 150 ± 10 mg; 200 ± 40 mg; or 200 ± 15 mg of tenofovir alafenamide hemifumarate is administered.

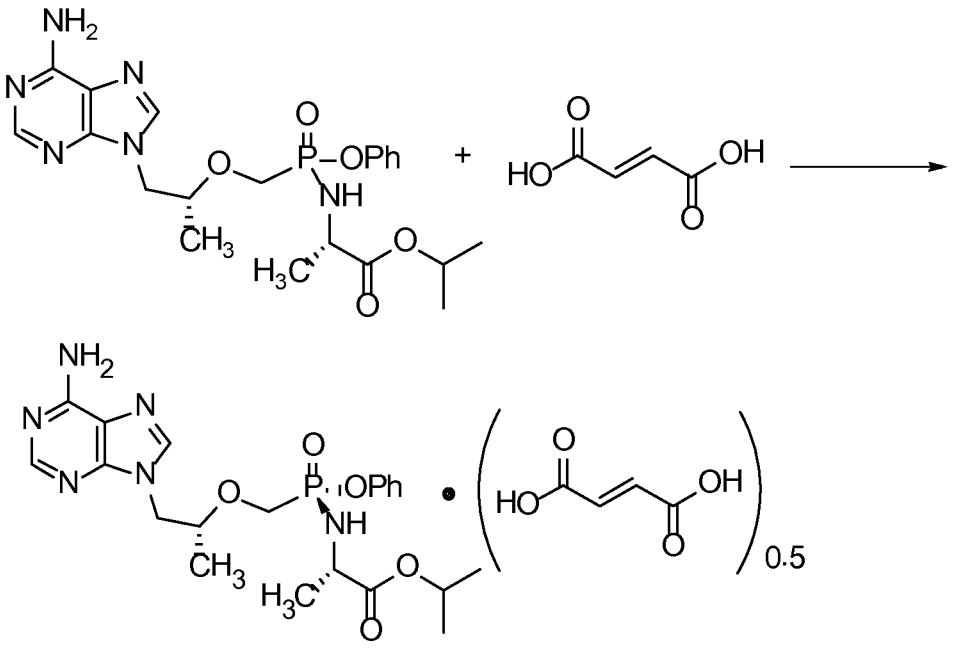
[0237] The desired daily dose of tenofovir alafenamide hemifumarate also may be administered as two, three, four, five, six, or more subdoses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0238] The concentration of tenofovir, GS-7340, or tenofovir alafenamide hemifumarate in the bloodstream may be measured as the plasma concentration (e.g., ng/mL). Pharmacokinetic parameters for determining the plasma concentration include, but are not limited to, the maximum observed plasma concentration (C_{max}), observed plasma concentration at the end of the dosing interval or "trough" concentration (C_{tau} or C_{min}), area under the plasma concentration time curve (AUC) from time zero up to the last quantifiable time point ($AUC_{0\text{-}last}$), AUC from time zero to infinity ($AUC_{0\text{-}inf}$), AUC over the dosing interval (AUC_{tau}), time of maximum observed plasma concentration after administration (t_{max}), and half-life of tenofovir, GS-7340, or tenofovir alafenamide hemifumarate in plasma ($t_{1/2}$).

[0239] Administration of GS-7340 or tenofovir alafenamide hemifumarate with food according to the methods of the invention may also increase absorption of GS-7340 or tenofovir alafenamide hemifumarate. Absorption of GS-7340 or tenofovir alafenamide hemifumarate may be measured by the concentration attained in the bloodstream over time after administration of GS-7340 or tenofovir alafenamide hemifumarate. An increase in absorption by administration of GS-7340 or tenofovir alafenamide hemifumarate with food may also be evidenced by an increase in C_{max} and/or AUC of GS-7340 or tenofovir alafenamide hemifumarate as compared to the values if GS-7340 or tenofovir alafenamide hemifumarate was administered without food. Typically protease inhibitors are administered with food.

Selective Crystallization – Tenofovir alafenamide hemifumarate

[0240] In one embodiment, tenofovir alafenamide hemifumarate can be prepared using selective crystallization. An example of a scheme for this preparation method is as follows.



[0241] The method can be carried out by subjecting a solution comprising: a) a suitable solvent; b) fumaric acid; c) tenofovir alafenamide; and, optionally, d) one or more seeds comprising tenofovir alafenamide hemifumarate, to conditions that provide for the crystallization of fumaric acid and tenofovir alafenamide. The starting solution can contain the single diastereomer of tenofovir alafenamide or a mixture of tenofovir alafenamide and one or more of its other diastereomers (e.g., GS-7339, as described in U.S. Patent No. 7,390,791).

[0242] The selective crystallization can be carried out in any suitable solvent. For example, it can be carried out in a protic solvent or in an aprotic organic solvent, or in a mixture thereof. In one embodiment, the solvent comprises a protic solvent (e.g., water or isopropyl alcohol). In another embodiment, the solvent comprises an aprotic organic solvent (e.g., acetone, acetonitrile (ACN), toluene, ethyl acetate, isopropyl acetate, heptane, tetrahydrofuran (THF), 2-methyl THF, methyl ethyl ketone, or methyl isobutyl ketone, or a mixture thereof). In one embodiment, the

solvent comprises ACN or a mixture of ACN and up to about 50% methylene chloride (by volume). The selective crystallization also can be carried out at any suitable temperature, for example, a temperature in the range of from about 0 °C to about 70 °C. In one specific embodiment, the resolution is carried out at a temperature of about 0 °C.

[0243] One major advantage of the hemifumarate form of tenofovir alafenamide over the monofumarate form is its exceptional capability to purge GS-7339 (i.e., 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine; described in, e.g., U.S. Patent No. 7,390,791), which is the major diastereomeric impurity in the active pharmaceutical ingredient. Thus, the hemifumarate form of tenofovir alafenamide can be more readily and easily separated from impurities than the monofumarate form. Other major advantages of tenofovir alafenamide hemifumarate over the monofumarate form include improved thermodynamic and chemical stability (including long-term storage stability), superior process reproducibility, superior drug product content uniformity, and a higher melting point.

[0244] Tenofovir alafenamide hemifumarate is useful in the treatment and/or prophylaxis of one or more viral infections in man or animals, including infections caused by DNA viruses. RNA viruses, herpesviruses (e.g., CMV, HSV 1, HSV 2, VZV), retroviruses, hepadnaviruses (e.g., HBV), papillomavirus, hantavirus, adenoviruses and HIV. U.S. Patent No. 6,043,230 (incorporated by reference herein in its entirety) and other publications describe the anti-viral specificity of nucleotide analogs, such as tenofovir disoproxil. Like tenofovir disoproxil, tenofovir alafenamide is another prodrug form of tenofovir, and can be used in the treatment and/or prophylaxis of the same conditions.

[0245] Tenofovir alafenamide hemifumarate can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including ocular, buccal, and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural). Generally, tenofovir alafenamide hemifumarate is administered orally, but it can be administered by any of the other routes noted herein.

[0246] Accordingly, pharmaceutical compositions include those suitable for topical or systemic administration, including oral, rectal, nasal, buccal, sublingual, vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal, and epidural) administration. The formulations are in unit dosage form and are prepared by any of the methods well known in the art of pharmacy.

[0247] For oral therapeutic administration, the tenofovir alafenamide hemifumarate may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions and preparations will typically contain at least 0.1% of tenofovir alafenamide hemifumarate. The percentage of this active compound in the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% or more of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful pharmaceutical compositions is preferably such that an effective dosage level will be obtained upon administration of a single-unit dosage (e.g., tablet). Other dosage formulations may provide therapeutically effective amounts of tenofovir alafenamide hemifumarate upon repeated administration of subclinically effective amounts of the same. Preferred unit dosage formulations include those containing a daily dose (e.g., a single daily dose), as well as those containing a unit daily subclinical dose, or an appropriate fraction thereof (e.g., multiple daily doses), of tenofovir alafenamide hemifumarate.

[0248] Pharmaceutical compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of tenofovir alafenamide hemifumarate; as a powder or granules; as a solution or a suspension in an aqueous liquid or a nonaqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. Tenofovir alafenamide hemifumarate may also be presented as a bolus, electuary, or paste.

[0249] Tenofovir alafenamide hemifumarate is preferably administered as part of a pharmaceutical composition or formulation. Such pharmaceutical composition or formulation comprises tenofovir alafenamide hemifumarate together with one or

more pharmaceutically acceptable carriers / excipients, and optionally other therapeutic ingredients. The excipient(s) / carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient. Excipients include, but are not limited to, substances that can serve as a vehicle or medium for tenofovir alafenamide hemifumarate (e.g., a diluent carrier). They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet.

[0250] Accordingly, the tablets, troches, pills, capsules, and the like may also contain, without limitation, the following: a binder(s), such as hydroxypropyl cellulose, povidone, or hydroxypropyl methylcellulose; a filler(s), such as microcrystalline cellulose, pregelatinized starch, starch, mannitol, or lactose monohydrate; a disintegrating agent(s), such as croscarmellose sodium, cross-linked povidone, or sodium starch glycolate; a lubricant(s), such as magnesium stearate, stearic acid, or other metallic stearates; a sweetening agent(s), such as sucrose, fructose, lactose, or aspartame; and/or a flavoring agent(s), such as peppermint, oil of wintergreen, or a cherry flavoring. When the unit dosage form is a capsule, it may contain, in addition to materials of the above types, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, polymers, wax, shellac, or sugar and the like. Of course, any material used in preparing any unit dosage form typically will be pharmaceutically acceptable and substantially nontoxic in the amounts employed. In addition, tenofovir alafenamide hemifumarate may be incorporated into sustained-release preparations and devices.

[0251] For infections of the eye or other external tissues, e.g., mouth and skin, the pharmaceutical compositions are preferably applied as a topical ointment or cream containing tenofovir alafenamide hemifumarate in an amount of, for example, 0.01 to 10% w/w (including active ingredient in a range between 0.1% and 5% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 3% w/w and most preferably 0.5 to 2% w/w. When formulated in an ointment,

the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base.

[0252] Pharmaceutical compositions suitable for topical administration in the mouth include lozenges comprising tenofovir alafenamide hemifumarate in a flavored basis, for example, 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.

[0253] Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

[0254] Pharmaceutical formulations suitable for parenteral administration are sterile and include aqueous and nonaqueous injection solutions that may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions that 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 with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier (e.g., water for injections) immediately prior to use. Injection solutions and suspensions may be prepared from sterile powders, granules, and tablets of the kind previously described.

[0255] In addition to the ingredients particularly mentioned above, the pharmaceutical compositions / formulations may include other ingredients conventional in the art, having regard to the type of formulation in question.

[0256] In another embodiment, there is provided veterinary compositions comprising tenofovir alafenamide hemifumarate together with a veterinary carrier therefor. Veterinary carriers are materials useful for the purpose of administering the composition to cats, dogs, horses, rabbits, and other animals, and may be solid, liquid, or gaseous materials that 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.

[0257] The tenofovir alafenamide hemifumarate can be used to provide controlled release pharmaceutical formulations containing a matrix or absorbent material and an active ingredient of the invention, 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 the compound. Controlled release formulations adapted for oral administration, in which discrete units comprising a compounds of the invention, can be prepared according to conventional methods.

[0258] Useful dosages of tenofovir alafenamide hemifumarate can be determined by comparing *in vitro* activities, and the *in vivo* activities in animal models. Methods for the extrapolation of effective amounts / dosages in mice and other animals to therapeutically effective amounts / dosages in humans are known in the art.

[0259] The amount of tenofovir alafenamide hemifumarate required for use in treatment will vary with several factors, including but not limited to the route of administration, the nature of the condition being treated, and the age and condition of the patient; ultimately, the amount administered will be at the discretion of the attendant physician or clinician. The therapeutically effective amount / dose of tenofovir alafenamide hemifumarate depends, at least, on the nature of the condition being treated, any toxicity or drug interaction issues, whether the compound is being used prophylactically (e.g., sometimes requiring lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

[0260] In one embodiment, the oral dose of tenofovir alafenamide hemifumarate may be in the range from about 0.0001 to about 100 mg/kg body weight per day, for example, from about 0.01 to about 10 mg/kg body weight per day, from about 0.01 to about 5 mg/kg body weight per day, from about 0.5 to about 50 mg/kg body weight per day, from about 1 to about 30 mg/kg body weight per day, from about 1.5 to about 10 mg/kg body weight per day, or from about 0.05 to about 0.5 mg/kg body weight per day. As a nonlimiting example, the daily candidate dose for an adult human of about 70 kg body weight will range from about 0.1 mg to about 1000 mg, or from about 1 mg to about 1000 mg, or from about 5 mg to

about 500 mg, or from about 1 mg to about 150 mg, or from about 5 mg to about 150 mg, or from about 5 mg to about 100 mg, or about 10 mg, and may take the form of single or multiple doses. In one embodiment, the oral dose of tenofovir alafenamide hemifumarate may be in the form of a combination of agents (e.g., tenofovir alafenamide hemifumarate / emtricitabine / elvitegravir / cobicistat).

[0261] The pharmaceutical compositions described herein may further include one or more therapeutic agents in addition to tenofovir alafenamide hemifumarate. In one specific embodiment of the invention, the additional therapeutic agent can be selected from the group consisting of HIV protease inhibiting compounds, HIV nonnucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

[0262] Therapeutic methods include administering tenofovir alafenamide hemifumarate to a subject / patient in need of the same as a therapeutic or preventative treatment. Thus, tenofovir alafenamide hemifumarate may be administered to a subject / patient having a medical disorder or to a subject who may acquire the disorder. One of ordinary skill will appreciate that such treatment is given in order to ameliorate, prevent, delay, cure, and/or reduce the severity of a symptom or set of symptoms of a disorder (including a recurring disorder). The treatment may also be given to prolong the survival of a subject, e.g., beyond the survival time expected in the absence of such treatment. The medical disorders that may be treated with tenofovir alafenamide hemifumarate include those discussed herein, including without limitation, HIV infection (including, without limitation, HIV-1 and HIV-2 infections; preferably HIV-1 infection) and HBV infection.

Formulation of Cobicistat

[0263] When cobicistat or a pharmaceutically acceptable salt thereof is combined with certain specific solid carrier particles (e.g. silica derivatives), the resulting combination possesses improved physical properties. Even though cobicistat is hygroscopic in nature, the resulting combination has comparatively low hygroscopicity. Additionally, the resulting combination is a free-flowing powder,

with high loading values for cobicistat, acceptable physical and chemical stability, rapid drug release properties, and excellent compressibility. Thus, the resulting combination can readily be processed into solid dosage forms (e.g. tablets), which possess good drug release properties, low tablet friability, good chemical and physical stability, and a low amount of residual solvents. The compositions of the invention represent a significant advance that facilitates the commercial development of cobicistat for use in treating viral infections such as HIV.

[0264] Cobicistat can be combined with any suitable solid carrier, provided the resulting combination has physical properties that allow it to be more easily formulated than the parent compound. For example, suitable solid carriers include kaolin, bentonite, hectorite, colloidal magnesium-aluminum silicate, silicon dioxide, magnesium trisilicate, aluminum hydroxide, magnesium hydroxide, magnesium oxide and talc. In one embodiment of the invention, the solid carrier can comprise calcium silicate (such as ZEOPHARM), or magnesium aluminometasilicate (such as NEUSILIN). As used herein, "loaded" on a solid carrier includes, but is not limited to a compound being coated in the pores and on the surface of a solid carrier.

[0265] Suitable silica derivatives for use in the compositions of the invention and methods for preparing such silica derivatives include those that are described in international patent application publication number WO 03/037379 and the references cited therein. A specific silica material that is particularly useful in the compositions and methods of the invention is AEROPERL® 300 (fumed silica), which is available from Evonik Degussa AG, Dusseldorf, Germany. Other materials having physical and chemical properties similar to the silica materials described herein can also be used.

Ritonavir

[0266] Ritonavir (1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[(2S)-3-methyl-2-{[methyl({[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl})carbamoyl]amino}butanamido]-1,6-diphenylhexan-2-yl]carbamate) was developed as an inhibitor of retroviral (HIV) protease; however, it is now used in a manner similar to cobicistat to inhibit the action of certain cytochrome P450

proteases (specifically Cyp3A4) thereby allowing greater circulating levels of drugs for treatment of HIV than would be obtained by administration of the drugs alone. Although none of GS-7340, tenofovir, or tenofovir alafenamide hemifumarate apparently is metabolized by cytochrome P450 proteases, it is contemplated that ritonavir may be used in the manner that cobicistat is used to boost the circulating levels of GS-7340, tenofovir, or tenofovir alafenamide hemifumarate, to improve the pharmacokinetics of GS-7340, tenofovir, or tenofovir alafenamide hemifumarate and achieve the other advantages of the use of cobicistat as disclosed herein.

Combination Treatment

[0267] The compounds and methods of the invention may also be used with any of the following compounds:

[0268] 1) amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, GS-8374, PPL-100, DG35, and AG 1859;

[0269] 2) an HIV nonnucleoside inhibitor of reverse transcriptase, e.g., capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

[0270] 3) an HIV nucleoside inhibitor of reverse transcriptase, e.g., zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-emtricitabine), D-d4FC, phosphazide, fozivudine tidoxil, apricitibine (AVX754), GS-7340, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003);

[0271] 4) an HIV nucleotide inhibitor of reverse transcriptase, e.g., tenofovir disoproxil fumarate and adefovir dipivoxil;

[0272] 5) an HIV integrase inhibitor, e.g., 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 phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011;

[0273] 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

[0274] 7) a CXCR4 inhibitor, e.g., AMD-070;

[0275] 8) an entry inhibitor, e.g., SP01A;

[0276] 9) a gp120 inhibitor, e.g., BMS-488043 or BlockAide/ CR;

[0277] 10) a G6PD and NADH-oxidase inhibitor, e.g., immunitin;

[0278] 11) a CCR5 inhibitor, e.g., aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

[0279] 12) other drugs for treating HIV, e.g., BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040);

[0280] 13) an interferon, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and pegylated IFN-beta;

[0281] 14) a ribavirin analog, e.g., rebetol, copegus, viramidine (taribavirin);

[0282] 15) an NS5b polymerase inhibitor, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433;

[0283] 16) an NS3 protease inhibitor, e.g., SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191;

[0284] 17) an alpha-glucosidase 1 inhibitor, e.g., MX-3253 (celgosivir), UT-231B;

[0285] 18) hepatoprotectants, e.g., IDN-6556, ME 3738, LB-84451, and MitoQ;

[0286] 19) a nonnucleoside inhibitor of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, GS-9190, and A-689; and

[0287] 20) other drugs for treating HCV, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

[0288] Exemplary combinations (including, but not limited to, single tablet regimens) include (a) emtricitabine / darunavir / cobicistat / GS-7340; (b) emtricitabine / darunavir / cobicistat / tenofovir alafenamide hemifumarate; (c) emtricitabine / darunavir / cobicistat / tenofovir disoproxil fumarate (TDF); (d) emtricitabine / elvitegravir / cobicistat / GS-7340; (e) emtricitabine / elvitegravir / cobicistat / tenofovir alafenamide hemifumarate; (f) emtricitabine / elvitegravir / cobicistat / TDF; (g) cobicistat / GS-7340; (h) cobicistat / tenofovir alafenamide hemifumarate; and (i) cobicistat / TDF. The combinations listed above may contain various dosages of the component agents; as nonlimiting examples, combination (b) above can include 200 mg of emtricitabine, 800 mg of darunavir, 150 mg of cobicistat, and 10 mg of tenofovir alafenamide hemifumarate, and combination (e) above can include 200 mg of emtricitabine, 150 mg of elvitegravir, 150 mg of cobicistat, and 10 mg of tenofovir alafenamide hemifumarate.

[0289] An alternative exemplary combination is emtricitabine and tenofovir alafenamide hemifumarate. The combination of emtricitabine and TDF is currently marketed as TRUVADA®. See also U.S. Patent Application Publication No. 2004/0224916, the content of which is hereby incorporated by reference herein in its entirety. The present invention provides the combination of emtricitabine and tenofovir alafenamide hemifumarate. This combination may contain various dosages of the two component agents; as a nonlimiting example, this combination can include 200 mg of emtricitabine and 10 mg of tenofovir alafenamide hemifumarate.

[0290] An additional alternative exemplary combination is emtricitabine, rilpivirine, and tenofovir alafenamide hemifumarate. The combination of emtricitabine, rilpivirine (a nonnucleoside reverse transcriptase inhibitor), and TDF is currently marketed as COMPLERA®. The present invention provides the

combination of emtricitabine, rilpivirine, and tenofovir alafenamide hemifumarate. This combination may contain various dosages of the three component agents; as a nonlimiting example, this combination can include 200 mg of emtricitabine, 25 mg of rilpivirine, and 10 mg of tenofovir alafenamide hemifumarate.

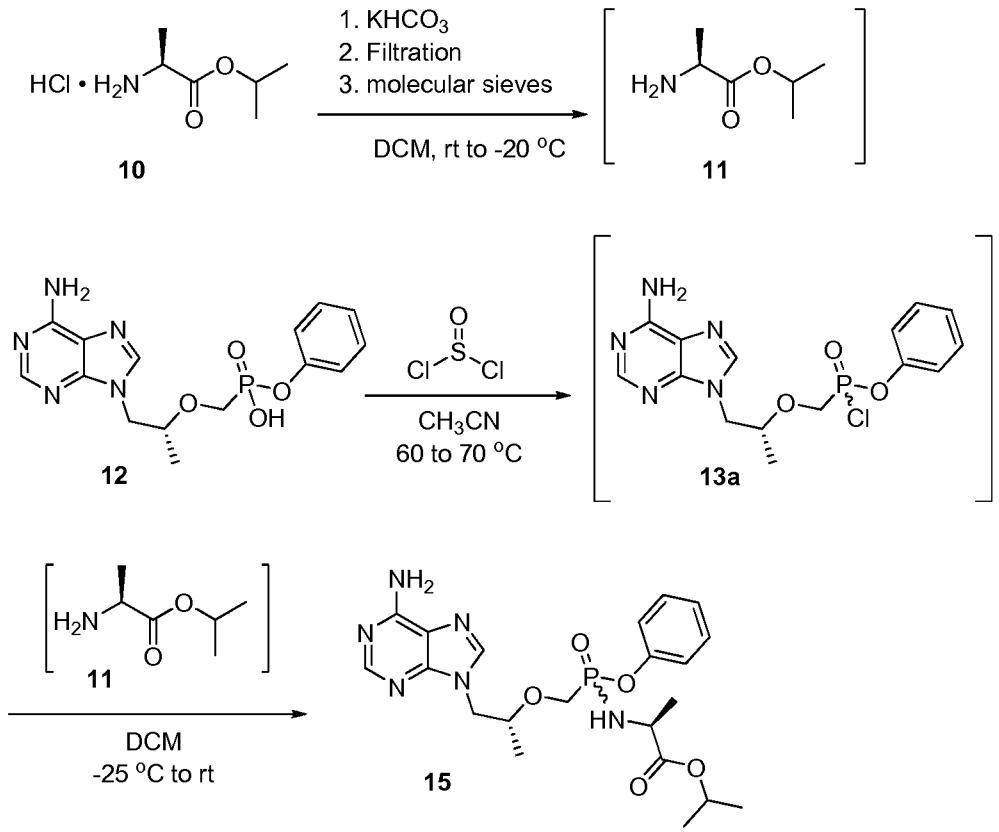
[0291] A further additional alternative exemplary combination is GS-9441 and tenofovir alafenamide hemifumarate. The combination of GS-9441 (a reverse transcriptase inhibitor) and GS-7340 is disclosed in U.S. Patent Application Publication No. 2009/0075939 and U.S. Patent No. 8,354,421, the content of each of which is hereby incorporated by reference herein in its entirety. The present invention provides the combination of GS-9441 and tenofovir alafenamide hemifumarate. This combination may contain various dosages of the two component agents; as a nonlimiting example, this combination can include 5-1500 mg of GS-9441 and 10 mg of tenofovir alafenamide hemifumarate.

[0292] Exemplary amounts of agents in various combinations include, but are not limited to, the following: (1) cobicistat: 10-500 mg, 50-500 mg, 75-300 mg, 100-200 mg, or 150 mg; (2) tenofovir alafenamide hemifumarate: 1-60 mg, 3-40 mg, 5-30 mg, 8-20 mg, or 10 mg; (3) emtricitabine: 10-500 mg, 50-500 mg, 75-300 mg, 150-250 mg, or 200 mg; (4) elvitegravir: 10-500 mg, 50-500 mg, 75-300 mg, 100-200 mg, or 150 mg; (5) darunavir: 300-1800 mg, 400-1600 mg, 500-1200 mg, 600-1000 mg, or 800 mg; and (6) rilpivirine: 5-100 mg, 10-80 mg, 15-60 mg, 20-40 mg, or 25 mg. One of skill in the art will know that, in the case of administering a pharmaceutically acceptable salt or complex of an agent, the amount administered will be adjusted relative to the weight of the component added to produce the salt or complex.

[0293] The invention will now be illustrated by the following nonlimiting Examples. The Synthetic Examples provided herein describe the synthesis of compounds of the invention as well as intermediates used to prepare compounds of the invention.

Synthetic Examples

Synthetic Example 1: Preparation of Diastereomeric Mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)**



a. Preparation of Compound **11**

[0294] Isopropyl L-alanine ester hydrochloride **10** (1 kg, 5.97 mol, 1.0 equiv) and potassium bicarbonate (1.45 kg, 14.5 mol, 2.43 equiv) were agitated in DCM (4 kg) for 10–14 hours with maximum agitation, maintaining the pot temperature between 19 and 25 °C. The mixture was then filtered and rinsed forward with DCM (2 kg). The filtrate was dried over a bed of 4 Å molecular sieves until the water content of the solution was $\leq$ 0.05%. The resultant stock solution containing compound **11** was then cooled to a pot temperature of -20 °C and held for further use.

b. Preparation of Compound **13a**

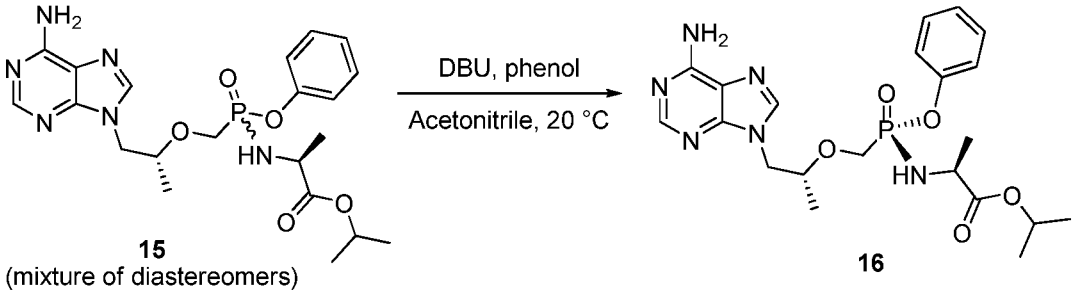
[0295] To a solution of thionyl chloride (0.72 kg, 6.02 mol, 2.19 equiv) in acetonitrile (5.5 kg) at 60 °C was added compound **12** (1 kg, 2.75 mol, 1.00 equiv) in 10 equal portions over 2 hours. The pot temperature was then adjusted to 70 °C and stirred for 1–3 hours until deemed complete by ^{31}P NMR analysis (Target: > 97.0 % conversion of starting material signal at 12.6 ppm to product signal at 22.0 ppm). The pot temperature was then adjusted to 40 °C and vacuum applied. The mixture was distilled to dryness, maintaining a maximum jacket temperature of 40 °C. The dry residue was then taken up in dichloromethane (30 kg) and the pot temperature adjusted to 19-25 °C. The resultant slurry containing compound **13a** was held for further use.

c. Preparation of Compound **15**

[0296] To the stock solution of isopropyl L-alanine ester **11** (4.82 equiv) at -25 °C was added slurry containing compound **13a** (1.0 equiv) over a minimum of 2 hours, maintaining the pot temperature ≤ -10 °C. The mixture was then held at a temperature ≤ -10 °C for at least 30 minutes, then the pH checked using water wet pH paper. If the pH was < 4, adjustment with triethylamine to pH 4–7 was performed. The pot temperature was then adjusted to room temperature (19-25 °C). In a separate vessel, a solution of sodium phosphate monobasic (2.2 kg, 18 mol, 6.90 equiv) in water (16 kg) was prepared. Half of the sodium phosphate monobasic solution was charged to the phosphonamidate reactor, and vigorously stirred. The layers were settled and partitioned. The organic layer was washed again with the remaining half of sodium phosphate monobasic solution. In a separate vessel, a solution of potassium bicarbonate (1.1 kg, 11 mol, 4.22 equiv) in water (5.5 kg) was prepared. Half of the potassium bicarbonate solution was charged to the organic phase, and vigorously stirred. The layers were settled and partitioned. The organic layer was washed again with the remaining half of the potassium bicarbonate solution followed by a final water (3.3 kg) wash. The organic phase was then retained and distilled to a volume of *ca.* 6 L. The resultant solution was analyzed for water content. If the water content was > 1.0%, DCM could be charged and the distillation to *ca.* 6 L repeated. When the solution water

content was less than or about 1.0%, the pot temperature was adjusted to 19-25 °C prior to discharge of the stock solution in DCM to provide the diastereomeric mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 – 1.33 (m, 12H), 3.62 – 3.74 (m, 1H), 3.86 – 4.22 (m, 5H), 4.30 – 4.44 (m, 1H), 4.83 – 5.10 (m, 1H), 6.02 (br s, 3H), 7.18 – 7.34 (m, 5H), 7.98 – 8.02 (m, 1H), 8.32 – 8.36 (m, 1H); ^{31}P NMR (162 MHz, $CDCl_3$): δ. 21.5, 22.9.

Synthetic Example 2: Crystallization-Induced Dynamic Resolution of Diastereomeric Mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)** to provide 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(16)**



[0297] A 22 wt% solution of diastereomeric mixture of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)** in acetonitrile (2.3 kg solution, 0.51 kg **15**, 1.1 mol, 1 equiv) was charged to a vessel equipped with an overhead stirrer, distillation apparatus, and nitrogen inlet. The mixture was concentrated by distillation at 100-300 mbar over a temperature range of 45-55 °C to a final concentration of 30-35 wt%. The distillation apparatus was then removed and the solution was cooled to 20 °C. The solution was seeded with 2.0% compound **16** and allowed to stir for one hour at 20 °C. Phenol (9.9 g, 0.11 mol, 0.1 equiv) and DBU (16 g, 0.11 mol, 0.1 equiv) were added and the mixture was stirred for an additional 24 hours or until the weight percent of compound **16** remaining in solution was less than 12%. The slurry was then

cooled to 0 °C and stirred for an additional 18 hours at 0 °C. The slurry was filtered and washed with a 1:1 solution of isopropyl acetate:acetonitrile (1.5 L) at 0 °C. The solids were dried in a vacuum oven at 50 °C to give 0.40 kg of compound **16** (80% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (m, 9H), 1.28 (d, *J* = 7.0 Hz, 3H), 3.65 (dd, *J*= 13.1, 10.7, 1H) 4.00 (m, 4H), 4.33 (dd, *J*= 14.4, 3.1 Hz, 1H), 5.00 (m, 1H) 6.00 (bs, 2H), 6.99 (m, 2H), 7.07 (m, 1H), 7.19 (m, 2H), 7.97 (s, 1H), 8.33 (s, 1H). ^{31}P NMR (162 MHz, $CDCl_3$): δ. 20.8.

Synthetic Example 3: Preparation of Compound **13a** in High Diastereomeric Purity

[0298] To a slurry of compound **12** (10.0 g, 27.5 mmol, 1.00 equiv) in toluene (60 mL) at ambient temperature was added thionyl chloride (3.0 mL, 41 mmol, 1.5 equiv). The slurry was heated to 70 °C and agitated for 48–96 hours until reaction and diastereomeric enrichment were deemed complete by HPLC (Target: > 97.0 % conversion of compound **12** to compound **13a** and > 90:10 diastereomeric ratio of compound **13a**). The mixture was concentrated to dryness by vacuum distillation, and the dry residue was taken up in toluene (50 mL). The resultant slurry containing compound **13a** was held at ambient temperature for further use.

Synthetic Example 4: Preparation of 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)** in High Diastereomeric Purity

[0299] To a solution of isopropyl L-alanine ester **11** (4.50 equiv) in DCM (80 mL) at -25 °C was added a slurry containing compound **13a** (1.00 equiv) that is at least 90% diastereomerically pure in toluene (50 mL) over a minimum of 45 minutes, maintaining the internal temperature ≤ -20 °C. The mixture was then held at a temperature ≤ -20 °C for at least 30 minutes, and the pH checked using water wet pH paper. If the pH was < 4, it was adjusted with triethylamine to pH 4-7. The pot temperature was adjusted to room temperature (19–25 °C). The mixture was transferred to a separatory funnel and washed sequentially with 10% w/v aqueous solution of sodium phosphate monobasic (2 x 50 mL), 15% w/v aqueous solution of potassium bicarbonate (2 x 20 mL), and water (50 mL). The

final organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a viscous amber oil. The oil was dissolved in toluene / acetonitrile (4:1) (50 mL), and the solution was seeded with 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine (about 1 mg, 99:1 diastereomeric ratio) and stirred for 2 hours at ambient temperature. The resultant slurry was filtered and the filter cake was washed with toluene / acetonitrile (4:1) (15 mL) and dried in a vacuum oven at 40 °C for 16 hours to give the product, 9-[(R)-2-[[(R,S)-1-[[(S)-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine **(15)**, as a white solid (10.0 g, 76.4%, 97.5:2.5 diastereomeric ratio). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 – 1.33 (m, 12H), 3.62 – 3.74 (m, 1H), 3.86 – 4.22 (m, 5H), 4.30 – 4.44 (m, 1H), 4.83 – 5.10 (m, 1H), 6.02 (br s, 3H), 7.18 – 7.34 (m, 5H), 7.98 – 8.02 (m, 1H), 8.32 – 8.36 (m, 1H); ^{31}P NMR (162 MHz, $CDCl_3$): δ. 21.5, 22.9.

Synthetic Example 5: Preparation of Compound **12**

[0300] PMPA (100.0 g, 0.35 mol, 1 equiv) was charged to a vessel equipped with an overhead stirrer, reflux condenser and nitrogen inlet followed by acetonitrile (800 mL). To the vessel was added triethylamine (71.0 g, 0.70 mol, 2 equiv) followed by DMAP (42.6 g, 0.35 mol, 1 equiv) and triphenylphosphite (162.1 g, 0.52 mol, 1.5 equiv). The mixture was heated to 80 °C and agitated for ≥ 48 hours at 80 °C or until the reaction was complete by ^{31}P NMR. (A sample directly from the reaction is taken and an insert containing 10% H_3PO_2 in D_2O is added. The intermediate formed is the PMPA anhydride and is at 6 ppm; the product is at 11 ppm. The reaction is deemed complete when less than 5% anhydride is present). The reaction mixture was distilled to ~1.5 volumes of acetonitrile and diluted with ethyl acetate (200 mL) and water (300 mL). The aqueous layer was separated and washed with ethyl acetate (200 mL) twice. The aqueous layer was recharged to the vessel and pH adjusted to pH 3 using 12.1 M HCl (21.0 mL). The reaction was then seeded with 0.05% of compound **12** seed and allowed to stir at 25 °C. Additional 12.1 M HCl was added over 20 minutes (7.0 mL) until pH 2 was achieved. The crystallization was allowed to stir at ambient temperature for

30 minutes and then cooled to 10°C over 2 hours. Once at 10°C the crystallization was allowed to stir for 2.5 hours at 10°C. The slurry was filtered and washed with pH 1.5 water (200 g). After drying in the vacuum oven, 102.2 g of compound **12** (81% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, D_2O): δ 1.31 (d, *J*= 6.1 Hz, 3H), 3.59 (dd, *J* = 14.0, 9.0 Hz, 1H), 3.85 (dd, *J*= 14.0, 9.0 Hz, 1H), 4.1 (m, 1H), 4.3 (dd, *J*= 15.0, 9.0 Hz, 1H), 4.5 (dd, *J*= 15.0, 2 Hz, 1H), 6.75 (d, *J*= 7 Hz, 2H), 7.15 (t, *J*= 7 Hz, 1H), 7.25 (t, *J*= 7 Hz, 2H), 8.26 (s, 1H), 8.35 (s, 1H). ^{31}P NMR (162 MHz, D_2O): δ. 14.8.

Synthetic Examples – Tenofovir alafenamide hemifumarate

Synthetic Example 6

[0301] Tenofovir alafenamide monofumarate solids (5.0 g) and 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine (GS-7339) monofumarate solids (0.75 g) were charged into 35 g MTBE at 22 °C and the mixture was stirred for 1 hour. A slurry was formed and was dried in a rotary evaporator. 58 g acetonitrile (ACN) was charged into the solids and the mixture was heated to reflux to dissolve the solids. The resulting solution was allowed to cool naturally while agitated. A slurry was formed, and the slurry was further cooled by an ice-water bath. The solids were isolated by filtration and washed with 5 g ACN. The solids were dried in a vacuum oven at 40 °C overnight. 5.52 g off-white solids were obtained. The solids were analyzed by XRPD and found to contain tenofovir alafenamide monofumarate, GS-7339 monofumarate, and tenofovir alafenamide hemifumarate.

Synthetic Example 7: Preparation of Tenofovir Alafenamide Hemifumarate via Selective Crystallization

[0302] 9-[(R)-2-[[[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine as a slurry in ACN (9.7 kg slurry, 13.8 wt%, a diastereomeric mixture of 1.0 kg (2.10 mol, 1 mol equiv) of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine

and 0.35 kg of 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine was charged into a reactor and rinsed forward with dichloromethane (5 kg). The mixture was concentrated under vacuum to about 3 L with jacket temperature below 40 °C. The concentrate was then coevaporated with ACN (6 kg) under vacuum to about 3 L with jacket temperature below 40 °C. The concentrate was diluted with ACN (8.5 kg) and warmed to 40-46 °C. The warm mixture was filtered into a second reactor and the filtrate was cooled to 19-25 °C.

[0303] To the above solution was charged fumaric acid (0.13 kg, 1.12 mol, 0.542 mole equiv) followed by ACN (1 kg), and the mixture was heated to 67-73 °C. The hot mixture was transferred into a reactor via a polishing filter, and then adjusted to 54-60 °C. Seed crystals (5 g) of the hemifumarate form of tenofovir alafenamide were charged (for example, the mixture can be seeded with tenofovir alafenamide hemifumarate formed in Synthetic Example 6 or a subsequent production), and the resulting mixture was agitated at 54-60 °C for about 30 minutes. The mixture was cooled over a minimum of 4 hours to 0-6 °C, and then agitated at 0-6 °C for a minimum of 1 hour. The resulting slurry was filtered and rinsed with chilled (0-6 °C) ACN (2 kg). The product was dried under vacuum below 45 °C until loss on drying (LOD) and organic volatile impurities (OVI) limits were met (LOD ≤ 1.0%, dichloromethane content ≤ 0.19%, acetonitrile content ≤ 0.19%) to afford the final compound of the hemifumarate form of tenofovir alafenamide as a white to off-white powder (typical yield is about 0.95 kg). ^{1}H NMR (400 MHz, d6 DMSO): δ 1.06 (d, J = 5.6 Hz, 3H), 1.12-1.16 (m, 9H), 3.77 (dd, J = 10.4, 11.6 Hz, 1H), 3.84-3.90 (m, 2H), 3.94 (m, 1H), 4.14 (dd, J = 6.8, 14.8 Hz, 1H), 4.27 (m, 1H), 4.85 (heptet, J = 6.0 Hz, 1H), 5.65 (t, J = 11.2 Hz, 1H), 6.63 (s, 1H), 7.05 (d. J = 7.6 Hz, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.24 (s, 2H), 7.29 (t, J = 7.6 Hz, 2H), 8.13 (t, J = 13.6 Hz, 2H), ^{31}P NMR (162 MHz, d6 DMSO): δ 23.3.

Synthetic Example 8: Preparation of Tenofovir Alafenamide Hemifumarate

[0304] To a jacketed reactor equipped with overhead agitator, was charged 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine

(10 g), fumaric acid (1.22 g), and ACN (100 mL). The mixture was heated to 70-75 °C to dissolve the solids. Any undissolved particulates were removed by filtration through a cartridge filter. The filtered solution was cooled to 60-65 °C, and seeded with 1% (by weight) of tenofovir alafenamide hemifumarate. The slurry was aged for 30 minutes and cooled to 0-5 °C over 2 hours. The temperature was maintained for 1-18 hours, and the resulting slurry was filtered and washed with 2 ml of cold ACN (0-5 °C). The solids were dried under vacuum at 50 °C to provide the hemifumarate form of tenofovir alafenamide, which was characterized as described below.

Characterization of Tenofovir Alafenamide Hemifumarate from Synthetic Example 8

[0305] Tenofovir alafenamide hemifumarate from Synthetic Example 8 consists of 9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine and one-half an equivalent of fumaric acid. Tenofovir alafenamide hemifumarate is anhydrous, nonhygroscopic, and has a DSC onset endotherm of about 131 °C.

X-ray Powder Diffraction

[0306] The XRPD pattern of tenofovir alafenamide hemifumarate was obtained in the following experimental setting: 45 KV, 45 mA, Kα1=1.5406 Å, scan range 2. - 40°, step size 0.0084°, counting time: 8.25 s. The XRPD pattern for tenofovir alafenamide hemifumarate is shown in Figure 13. The characteristic peaks include: 6.9 ± 0.2°, 8.6 ± 0.2°, 10.0 ± 0.2°, 11.0 ± 0.2°, 12.2 ± 0.2°, 15.9 ± 0.2°, 16.3 ± 0.2°, 20.2 ± 0.2°, and 20.8 ± 0.2°.

Single-Crystal X-ray Diffraction

[0307] The crystal size was 0.32 x 0.30 x 0.20 mm^3. The sample was held at 123 K and the data was collected using a radiation source with a wavelength of 0.71073 Å in the theta range of 1.59 to 25.39°. Conditions of, and data collected from the single-crystal X-ray diffraction are shown in Table 1.

Table 1. Single-Crystal X-ray Diffraction

Empirical formula	$C_{23}H_{31}N_6O_7P$
Formula weight	534.50
Temperature	123(2) K
Crystal size	0.32 x 0.30 x 0.20 mm^3
Theta range for data collection	1.59 to 25.39°
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	P4(2)2(1)2
Unit cell dimensions	a = 18.1185(12) Å α = 90° b = 18.1185(12) Å β = 90° c = 17.5747(11) Å γ = 90°
Volume	5769.4(6) $Å^3$
Z	8
Density (calculated)	1.231 g/cm^3

DSC Analysis

[0308] The DSC analysis was conducted using 2.517 mg of tenofovir alafenamide hemifumarate. It was heated at 10 °C/min over the range of 40-200 °C. The onset endotherm was found to be about 131 °C (Figure 14).

TGA Data

[0309] The TGA data were obtained using 4.161 mg of tenofovir alafenamide hemifumarate. It was heated at 10 °C/min over the range of 25-200 °C. The sample lost 0.3% weight before melting (Figure 15). It was determined to be an anhydrous form.

DVS Analysis

[0310] DVS analysis was conducted using 4.951 mg of tenofovir alafenamide hemifumarate. The material was kept at 25 °C in nitrogen at humidities ranging from 10% to 90% relative humidity; each step was equilibrated for 120 minutes.

The sorption isotherm is shown at Figure 16. The material was found to be nonhygroscopic, and to absorb 0.65% water at a relative humidity of 90%.

Purging of Diastereomeric Impurity

[0311] In the prior syntheses of tenofovir alafenamide, one of the major impurities is typically the diastereomer 9-[(R)-2-[[(R)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine. The hemifumarate form of tenofovir alafenamide from Synthetic Example 8 has an exceptional capability to purge this diastereomeric impurity, as compared with the capability of the monofumarate form (described in, e.g., U.S. Patent No. 7,390,791). The data in Table 2 (below) demonstrates that tenofovir alafenamide hemifumarate (Batch 2) purged the diastereomeric impurity to less than one-tenth of the starting concentration, whereas the monofumarate form of tenofovir alafenamide (Batch 1) only slightly purged the diastereomeric impurity.

Table 2. Purging Capability Comparison

Batch	Diastereomeric Impurity in Starting Material	Solvent	Fumaric acid charge (mole equivalent)	Product obtained	Diastereomeric Impurity in Product
1	9.3%	ACN	0.9	Monofumarate form	7.6%
2	10.0%	ACN	0.5	Hemifumarate form	0.65%

Chemical Stability

[0312] Chemical stability of the hemifumarate form of tenofovir alafenamide was compared with the monofumarate form. As shown in Table 3 (below), under identical conditions, the hemifumarate form of tenofovir alafenamide was chemically more stable and exhibited better long-term storage stability, with significantly less degradation (% Total Deg. Products) than the monofumarate form. Conditions evaluated include temperature, relative humidity (RH), and the open or closed state of the container cap.

Table 3. Chemical Stability Comparison

Storage Condition	Time Points (weeks)	Monofumarate form		Hemifumarate form	
		% TA* Area Normalized	% Total Deg. Products	% TA Area Normalized	% Total Deg. Products
40°C / 75% RH Cap Closed	0	97.1	0.69	98.4	0.05
	1	97.0	0.87	98.4	0.14
	2	96.6	1.18	98.5	0.14
	4	96.4	1.49	98.4	0.25
	8	95.4	2.36	98.0	0.49
40°C / 75% RH Cap Open	0	97.1	0.69	98.4	0.05
	1	96.9	0.90	98.5	0.15
	2	96.6	1.10	98.5	0.14
	4	96.2	1.67	98.4	0.26
	8	95.0	2.74	98.1	0.50
70°C Cap Closed	0	97.1	0.69	98.4	0.05
	2	96.2	1.83	98.5	0.22
	4	93.3	4.78	98.4	0.33

*TA is tenofovir alafenamide

Thermodynamic Stability

[0313] Stable form screening of tenofovir alafenamide hemifumarate showed that it is thermodynamically stable in most solvents, such as ACN, toluene, ethyl acetate, methyl *tert*-butyl ether (MTBE), acetone, THF, and 2-methyl THF. A similar stable form screening of the monofumarate form showed that this form is not thermodynamically stable in the above-listed solvents. When suspended in these solvents, the monofumarate form of tenofovir alafenamide fully converts to the hemifumarate form in THF and 2-methyl THF, and partially converts to the hemifumarate form in ACN, ethyl acetate, MTBE, and acetone, as well as at ambient temperatures.

Thermal Stability

[0314] As shown by the DSC data, the hemifumarate form of tenofovir alafenamide has a melting point that is about 10 °C higher than that of the monofumarate form, indicating that the hemifumarate form has improved thermal stability as compared with the monofumarate form.

Biological Example 1: Transport Studies

[0315] Caco-2 transepithelial transport studies: Caco-2 cells between passage 43 and 69 were grown to confluence over at least 21 days on 24-well polyethylene-terephthalate (PET) transwell plates (BD Biosciences, Bedford, MA). Experiments were conducted using Hank's Buffered Salt Solution (HBSS) containing 10 mM HEPES and 15 mM Glucose obtained from Life Technologies (Grand Island, NY). Donor and receiver buffers had their pH adjusted to pH 6.5 and 7.4, respectively. The receiver well used HBSS buffer supplemented with 1% bovine serum albumin. In studies done to determine transport inhibition, monolayers were preincubated for 60 minutes in the presence of assay buffer and inhibitor in order to saturate any transporter binding sites. Following preincubation, fresh assay buffer containing inhibitor and the test compound were added. Test compound concentrations in assay chambers were analyzed by liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS). Transepithelial electrical resistance (TEER) and lucifer yellow permeability were determined to assure membrane integrity. Each individual experiment was done in duplicate and the permeation of control compounds atenolol (low permeability), propranolol (high permeability), and vinblastine (efflux transport) were determined to meet acceptance criteria for each batch of assay plates.

[0316] Pgp and BCRP inhibition assays in transfected Madin-Darby canine kidney (MDCKII) cells: Inhibition of Pgp-mediated transport was studied using the Pgp substrate calcein AM and MDCKII cells transfected with the human MDR1 (ABCB1) gene (encoding Pgp). Similarly, inhibition of BCRP-mediated transport was studied using the BCRP substrate Hoechst 33342 and MDCKII cells transfected with the human ABCG2 gene (encoding BCRP). Briefly, MDCKII cells were seeded in 96-well black cell culture plates with clear bottoms at a density of 5×10^4 cells/well and grown to confluence overnight. Test compounds were diluted in cell culture medium containing 10 μM Hoechst 33342 and incubated for 3 hours with MDCKII-BCRP and nontransfected cells. Following removal of media containing Hoechst 33342 and test compound, cells were washed twice with warm medium and lysed at room temperature for 5-10 minutes in a buffer containing 20 mM Tris-HCl pH 9.0 and 0.4% Triton X-100. Wells were

analyzed for Hoechst 33342 fluorescence at an excitation of 353 nm and an emission of 460 nm.

[0317] Pgp and BCRP substrate assays in transfected MDCKII cells: MDCKII cells were grown to confluence over 4-6 days on 24-well PET transwell plates (BD Biosciences). The same buffers were used in the donor and receiver wells as described above for caco-2 studies. Experiments were conducted as described above for caco-2 transepithelial transport studies and samples analyzed by LC/MS/MS. Similar quality control and acceptance criteria were used as those described above for caco-2 studies. TEER values and the permeability of lucifer yellow, atenolol, and propranolol were determined to meet acceptance criteria for each batch of assay plates. Efflux ratios were determined to be at least 3-fold higher in transfected versus nontransfected monolayers for the model Pgp substrate vinblastine and BCRP substrate prazosin.

[0318] Data analysis: The 50% inhibition constants (IC_{50}) values for transporters in the fluorescent accumulation studies done in MDCKII cells, defined as the test article concentration needed to inhibit the maximal transporter specific transport by 50%, were calculated using nonlinear curve fitting of inhibition versus concentration to a sigmoidal curve with a variable Hill coefficient using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA). Apparent permeability coefficients and efflux ratios (ER) from transcellular experiments in caco-2 or MDCKII cells were calculated as previously described (Tong et al. (2007) *Antimicrob Agents Chemother* 51:3498-504). Where appropriate, the statistical significance of differences observed between test conditions was assessed using paired two-tailed Student's *t* tests.

[0319] Inhibition of Pgp and BCRP in transfected MDCKII cells: The inhibition of Pgp and BCRP by cobicistat relative to ritonavir and the known transport inhibitors cyclosporin A (CSA) and fumitremorgin C was studied by monitoring the effects of coincubation on the Pgp- and BCRP-dependent accumulation of the fluorescent probe substrates calcein AM and Hoechst 33342 in MDCKII-MDR1 and MDCKII-ABCG2 cells, respectively. Cobicistat inhibited Pgp and BCRP with IC_{50} values of 36 ± 10 μM and 59 ± 28 μM, respectively. Ritonavir, when incubated at its approximate solubility limit in assay buffers (20 μM) showed 35%

inhibition of Pgp and 21% inhibition of BCRP. Higher concentrations of cobicistat were achievable in assays because of its > 35-fold higher aqueous solubility at neutral pH. Greater differences in the concentrations of cobicistat and ritonavir may exist in the gastrointestinal (GI) tract based on their respective solubility under acidic conditions. Taken together, the solubility and inhibition results indicate that cobicistat should have similar inhibition of Pgp and BCRP in the GI tract relative to ritonavir.

[0320] Pgp and BCRP substrate assays in transfected MDCKII cells: To further characterize the mechanism interaction of cobicistat with Pgp (multidrug resistance protein 1; MDR1) and BCRP, bidirectional permeability assays were completed in cells transfected with the genes for the human transport proteins to determine if cobicistat is a substrate for these efflux transporters (Figure 10). Bidirectional permeability of cobicistat (10 μM) was assessed in MDCKII-WT, MDCKII-MDR1 (Figure 10A) and MDCKII-BCRP cells (Figure 10B). The black bars show apical to basolateral (A-B) permeability, and the open bars show basolateral to apical (B-A) permeability. Efflux ratios are indicated above graphs for each experimental condition. CSA (10 μM) and Ko134 (10 μM) were used as known inhibitors of Pgp and BCRP, respectively. Results are the average of duplicate wells from a representative side by side experiment done comparing wild type MDCKII (MDCKII-WT) to MDCKII-MDR1 or MDCKII-BCRP cells in the presence or absence of respective inhibitors. The overexpression of Pgp or BCRP in MDCKII cells increased the efflux ratios of cobicistat. These increased efflux ratios reflected a decrease in the forward permeability and an increase in the reverse permeability of cobicistat. Consistent with Pgp- and BCRP-dependent transport, cobicistat efflux was decreased in the presence of the Pgp inhibitor CSA and the BCRP inhibitor Ko134. These results illustrate that cobicistat is a substrate for both Pgp and BCRP, suggesting that the observed inhibition may be due to competition for the binding sites of the respective transporters.

[0321] Effect of cobicistat on the bidirectional permeability of model Pgp and BCRP substrates through caco-2 cell monolayers: Caco-2 cells have been reported as a physiologically relevant model system of GI absorption that supports the polarized expression of intestinal transporters including Pgp and BCRP. The effect

of cobicistat (COBI; 90 μM) and ritonavir (RTV; 20 μM) on the bidirectional permeability through monolayers of caco-2 cells of 10 μM of the Pgp substrate digoxin (Figure 11A) and BCRP substrate prazosin (Figure 11B) were studied. Digoxin and prazosin were chosen as model substrates of Pgp and BCRP, respectively, based on recommendations from the FDA and by the International Transporter Consortium. The known Pgp inhibitor CSA (10 μM) and BCRP inhibitor fumitremorgin C (2 μM; noted in Figure 11B as "FTC") were used as positive controls. The black bars show apical to basolateral (A-B) and the open bars basolateral to apical (B-A) permeability, and efflux ratios are indicated above graphs for each experimental condition. Results are the mean ± standard deviation of at least four independent experiments done in duplicate, and statistical significance was assessed by comparing results to no cotreatment wells using paired two-tailed Student's *t* tests (*, $P < 0.05$; **, $P < 0.01$). Similar to the known Pgp inhibitor CSA, cobicistat and ritonavir markedly reduced the efflux ratio and significantly increased the apical to basolateral (A-B) permeability of digoxin (Figure 11A). Similar effects were observed in experiments studying the effect of cobicistat and ritonavir relative to the known BCRP inhibitor fumitremorgin C on the permeability of the BCRP substrate prazosin (Figure 11B). These data suggest similar inhibitory effects of cobicistat and ritonavir on the Pgp-mediated transport of digoxin- and BCRP-mediated transport of prazosin.

[0322] Effect of cobicistat on the bidirectional permeability of HIV protease inhibitors and GS-7340 through caco-2 cell monolayers: The effect of cobicistat (90 μM) and ritonavir (20 μM) on the bidirectional permeability of the HIV protease inhibitors (PIs) atazanavir, darunavir, lopinavir, and GS-8374, an experimental HIV PI, through caco-2 cell monolayers was assessed. The effect of RTV and COBI was assessed with 10 μM of the HIV PIs atazanavir (Figure 12A), darunavir (Figure 12B), lopinavir (Figure 12C) and GS-8374 (Figure 12D). The black bars show apical to basolateral (A-B) and the open bars basolateral to apical (B-A) permeability, and efflux ratios are indicated above graphs for each experimental condition. Results are the mean ± standard deviation of at least four independent experiments done in duplicate, and statistical significance was assessed comparing directional results to no cotreatment wells by using paired two-

tailed Student's *t* tests (*, P <0.05; **, P<0.01; ***,P<0.001). The effect of COBI (90 μM) was assessed on the bidirection permeability of GS-7340 (10 μM) through caco-2 monolayers over a 2 hour time course in the A-B (Figure 12E) and B-A (Figure 12F) directions. Open symbols depict presence and solid symbols depict absence of COBI. Results are the mean ± standard deviation of duplicate measurements from two independent experiments. Consistent with previous studies reporting these compounds as Pgp substrates, significant efflux was observed for each of the protease inhibitors. Coadministration of cobicistat and ritonavir comparably reduced the efflux ratios by increasing the A-B flux and decreasing the B-A flux of the protease inhibitors (Figure 12A-D). The effect of cobicistat on GS-7340 permeability across caco-2 monolayers was monitored over 2 hours, and cobicistat increased the A-B flux of GS-7340 while concomitantly reducing B-A flux (Figure 12E-F).

[0323] These results support the hypothesis that cobicistat may be acting to inhibit Pgp-mediated intestinal secretion of GS-7340.

Biological Example 2

[0324] Pharmacokinetic studies were done in humans to determine exposure to GS-7340 at three dose levels. Eligible subjects were randomized to receive either GS-7340 dose of 8 mg, GS-7340 dose of 25 mg, GS-7340 dose of 40 mg, tenofovir (as TDF) 300 mg or placebo-to-match GS-7340 for 10 days. (Note: Doses of GS-7340 are given as the mass of free base of GS-7340, even where other forms of GS-7340 were dosed.) GS-7340 was administered in a blinded fashion, unless a subject was randomized to receive tenofovir which was given on an open-label basis.

[0325] Figure 1 shows tenofovir plasma concentrations in patients on Day 1 of the study. The top line (no symbol) shows the concentration of tenofovir in patients dosed with 300 mg tenofovir (as TDF). The next line down (triangles pointed down) shows the concentration of tenofovir in patients dosed with 40 mg GS-7340. The next line down (triangles pointed up) shows the concentration of tenofovir in patients dosed with 25 mg GS-7340. The bottom line (squares) shows the

concentration of tenofovir in patients dosed with 8 mg GS-7340. The table below the graph shows Cmax and AUC values obtained.

[0326] Figure 2 shows tenofovir plasma concentrations in patients on Day 10 of the study. The top line (diamonds) shows the concentration of tenofovir in patients dosed with 300 mg tenofovir. The next line down (triangles pointed down) shows the concentration of tenofovir in patients dosed with 40 mg GS-7340. The next line down (triangles pointed up) shows the concentration of tenofovir in patients dosed with 25 mg GS-7340. The bottom line (squares) shows the concentration of tenofovir in patients dosed with 8 mg GS-7340. The table below the graph shows Cmax and AUC values obtained.

Biological Example 3

[0327] Drug interaction potential between once-daily emtricitabine (FTC) / GS-7340 fixed dose combination, cobicistat boosted darunavir plus GS-7340 as a single agent, and efavirenz or cobicistat-boosted darunavir was evaluated in an open-label, crossover, single-center, multiple-dose, multiple-cohort study.

[0328] Table 4 shows the dosing regimen and schedule for the study.

Cohort 1 (n = 12)		
Cohort	Day 1–12	Day 13–26
	Treatment A: FTC/GS-7340 FDC (200/40 mg) administered once-daily in the morning under fasted condition	**Treatment B:** FTC/GS-7340 FDC (200/40 mg) plus efavirenz (EFV) 600 mg administered once-daily in the morning under fasted condition
Cohort 2 (n = 12)		
Cohort	Day 1–12	Day 13–22
	Treatment C: FTC/GS-7340 FDC (200/25 mg) administered once-daily in the morning under fed condition	**Treatment D:** FTC/GS-7340 FDC (200/25 mg) plus cobicistat-boosted darunavir (DRV/co; 800/150 mg) administered once-daily in the morning under fed condition
Cohort 3 (n = 14)		
Cohort	Day 1–10	Day 11–22
	Treatment E: Cobicistat boosted darunavir (DRV/co: 800/150 mg) administered once-daily in the morning under fed condition	**Treatment F:** FTC/GS-7340 FDC (200/25 mg) plus cobicistat boosted darunavir (DRV/co, 800/150 mg) administered once daily in the morning under fed condition
Cohort 4 (n = 12):		
Cohort	Day 1–12	Day 13–22
	Treatment G: GS-7340 (8 mg) single agent administered once daily in the morning under fed conditions	**Treatment H:** GS-7340 (8 mg) single agent PLUS cobicistat (150 mg) administered once daily in the morning under fed Conditions

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Table 4

[0329] Results of the pharmacokinetic analysis in this study are shown in Figures 3-5. (Note: Doses of GS-7340 are given as the mass of free base of GS-7340, even where other forms of GS-7340 were dosed.)

[0330] Figure 3A shows GS-7340 (tenofovir alafenamide) concentrations (ng/ml) for doses of emtricitabine and GS-7340 (triangles pointed up) and emtricitabine, GS-7340 and efavirenz ((initial value = 100 ng/ml); triangles pointed down) in patients from Cohort 1. Cmax and AUC results are displayed in the table below for GS-7340 exposure. Tenofovir (TFV) concentrations are shown in Figure 3B for doses of emtricitabine and GS-7340 (upper line; triangles pointed up) and emtricitabine, GS-7340 and efavirenz (lower line: triangles pointed down). Cmax and AUC results are displayed in the table below for tenofovir exposure.

[0331] Figure 4A shows GS-7340 concentrations (ng/ml) for doses of emtricitabine and GS-7340 (triangles pointed up) and emtricitabine, GS-7340, darunavir, and cobicistat (triangles pointed down) in patients from Cohort 2. C_{max} and AUC results are displayed in the table below for GS-7340 exposure. Tenofovir (TFV) concentrations are shown in Figure 4B for doses of emtricitabine and GS-7340 (triangles pointed up) and emtricitabine, GS-7340, darunavir, and cobicistat (triangles pointed down). C_{max} and AUC results are displayed in the table below for tenofovir exposure.

[0332] Figure 5A shows GS-7340 concentrations (ng/ml) for doses of GS-7340 alone and GS-7340 and cobicistat (triangles pointed up). C_{max} and AUC results are displayed in the table below for GS-7340 exposure. Tenofovir (TFV) concentrations are shown in Figure 5B for doses of GS-7340 alone (triangles pointed up) and GS-7340 and cobicistat (triangles pointed down). C_{max} and AUC results are displayed in the table below for tenofovir exposure.

[0333] Increases in exposures were observed for GS-7340 (tenofovir alafenamide) and TFV when dosed as GS-7340 (8 mg) plus COBI (150 mg) versus GS-7340 (8 mg) as a stand-alone agent. GS-7340 AUC_{last} and C_{max} were ~2.7- and 2.8-fold higher, respectively, whereas TFV AUC_{tau} and C_{max} were ~3.3- and 3.3-fold higher, respectively. These data suggest that the interaction is COBI-mediated, likely due to inhibition of Pgp-mediated intestinal secretion of tenofovir alafenamide (GS-7340).

Biological Example 4

[0334] GS-7340 and cobicistat were administered in conjunction with elvitegravir and emtricitabine in a clinical trial to determine the relative bioavailability of these compounds. The compounds were administered using a 25 mg or 40 mg dose of GS-7340 (test) relative to exposures (elvitegravir, cobicistat, emtricitabine) from elvitegravir/cobicistat/emtricitabine/tenofovir (reference) or GS-7340 (TFV) (reference). A second cohort with a similar design evaluated an alternate formulation of elvitegravir/cobicistat/emtricitabine/GS-7340 STR. (Note: Doses of Compound are given as the mass of free base of GS-7340, even where other forms of GS-7340 were dosed.) Elvitegravir/cobicistat/emtricitabine/GS-7340 (monolayer) tablets were manufactured by blending of emtricitabine/GS-7340 granulation with elvitegravir granulation and cobicistat, tablet compression, tablet film-coating, and packaging. Elvitegravir/cobicistat/emtricitabine/GS-7340 bilayer tablets are manufactured by compression of the elvitegravir/cobicistat layer and emtricitabine/GS-7340 layer, tablet film-coating, and packaging. In order to provide a robust assessment of pharmacokinetic comparisons between test versus reference treatments, a balanced Williams 4 x 4 design was used in each cohort.

[0335] The dose of elvitegravir (150 mg), the boosting dose of cobicistat (150 mg), and dosage of emtricitabine (200 mg) in elvitegravir/cobicistat/emtricitabine/GS-7340 represent current investigational doses (elvitegravir, cobicistat) or marketed dose (emtricitabine) with demonstrated durable efficacy and long-term safety in HIV-infected patients.

[0336] The evaluation used two cohorts of twenty patients. In Cohort 1, the following study treatments were administered.

[0337] **Treatment A:** 1 × Single Tablet Regimen (STR) of **Formulation 1** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 25 mg GS-7340 (as 31.1 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0338] **Treatment B:** 1 × STR **Formulation 1** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 40 mg GS-7340 (as 49.7 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0339] Treatment C: 1 × STR (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 300 mg tenofovir (as tenofovir disoproxil fumarate) QD, administered in A.M. for 12 days.

[0340] Treatment D: 1 × 25 mg GS-7340 tablet QD, administered in A.M. for 12 days.

[0341] Patients were randomized to one of four sequences (I, II, III, or IV).

	Day 1-12	Day 15-26	Day 29-40	Day 43-54
Sequence I	A	B	C	D
Sequence II	B	D	A	C
Sequence III	C	A	D	B
Sequence IV	D	C	B	A

[0342] Formulation 1 (monolayer) was prepared by blending of emtricitabine/GS-7340 granulation with elvitegravir granulation and cobicistat, tablet compression, tablet film-coating, and packaging. The EVG/COBI/FTC/GS-7340 STR tablet cores contain colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, and magnesium stearate as inactive ingredients and are film-coated with polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide.

[0343] In Cohort 2, the following study treatments were administered:

[0344] Treatment E: 1 × STR **Formulation 2** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 25 mg GS-7340 (as 31.1 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0345] Treatment F: 1 × STR **Formulation 2** (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 40 mg GS-7340 (as 49.7 mg of the fumarate salt GS-7340-02)) QD, administered in A.M. for 12 days.

[0346] Treatment C: 1 × STR (150 mg elvitegravir plus 150 mg cobicistat plus 200 mg emtricitabine plus 300 mg tenofovir) QD, administered in A.M. for 12 days.

[0347] Treatment D: 1 × 25 mg GS-7340 tablet QD, administered in A.M. for 12 days.

[0348] Patients were randomized to one of four sequences (I, II, III, or IV).

	Day 1-12	Day 15-26	Day 29-40	Day 43-54
Sequence I	E	F	C	D
Sequence II	F	D	E	C
Sequence III	C	E	D	F
Sequence IV	D	C	F	E

[0349] Formulation 2 was prepared as bilayer tablets that were manufactured by compression of the elvitegravir/cobicistat layer and emtricitabine/GS-7340 layer, tablet film-coating, and packaging. The EVG/COBI/FTC/GS-7340 STR tablet cores contain colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, and magnesium stearate as inactive ingredients and are film-coated with polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide.

[0350] Figure 6 shows pharmacokinetic data for GS-7340 from patients treated in Cohort 1 (Formulation 1, monolayer). The top line (triangles pointed down) shows GS-7340 concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The middle line (triangles pointed up) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (squares) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results show GS-7340 levels that are 2.2-fold higher for dosing at the 25 mg level when GS-7340 is administered with cobicistat.

[0351] Figure 7 shows pharmacokinetic data for GS-7340 from patients treated in Cohort 2 (Formulation 2, bilayer). The top line (triangles pointed down) shows GS-7340 concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The middle line (triangles pointed up) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (squares) shows GS-7340 concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results also show GS-7340 levels that are 2.2-fold higher for dosing at the 25 mg level when GS-7340 is administered with cobicistat.

[0352] Figure 8 shows pharmacokinetic data for tenofovir from patients treated in Cohort 1 (Formulation 1, monolayer). The top line (no symbol) shows tenofovir concentration (ng/ml) when 300 mg tenofovir is administered with cobicistat. The

next line down (triangles pointed up) shows tenofovir concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The next line down (squares) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (triangles pointed down) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results also show tenofovir levels that are 3-4 fold higher for dosing at the 25 mg level when tenofovir or GS-7340 is administered with cobicistat.

[0353] Figure 9 shows pharmacokinetic data for tenofovir from patients treated in Cohort 2 (Formulation 2, bilayer). The top line (circles) shows tenofovir concentration (ng/ml) when 300 mg tenofovir is administered with cobicistat. The next line down (triangles pointed up) shows tenofovir concentration (ng/ml) when 40 mg GS-7340 is administered with cobicistat. The next line down (squares) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered with cobicistat. The bottom line (triangles pointed down) shows tenofovir concentration (ng/ml) when 25 mg GS-7340 is administered alone. These results also show GS-7340 levels that are 3-4 fold higher for dosing at the 25 mg level when tenofovir or GS-7340 is administered with cobicistat.

[0354] Following administration of EVG/COBI/FTC/GS-7340 (25 mg) Formulations 1 and 2, geometric mean GS-7340 and TFV exposures were substantially higher, relative to GS-7340 (25 mg) as a stand-alone agent. With both formulations of EVG/COBI/FTC/GS-7340 (25 mg), GS-7340 AUC_{last} and C_{max} were ~2.2- and 2.3-fold higher, respectively, whereas TFV AUC_{tau} and C_{max} were ~3.1- and 3.7-fold higher, respectively. GS-7340 and TFV exposures were generally dose-proportional following EVG/COBI/FTC/GS-7340 (40 mg) versus EVG/COBI/FTC/GS-7340 (25 mg).

Biological Example 5

[0355] GS-7340 was coformulated with elvitegravir (EVG), cobicistat (COBI), and emtricitabine (FTC) into a single tablet regimen (STR). Across three healthy subject studies, the multiple dose pharmacokinetics (PK) of EVG/COBI/FTC/GS-7340 STR and/or interaction potential between GS-7340 and

COBI were evaluated to facilitate GS-7340 dose selection for STR clinical development.

[0356] In Study 1 (n=20), subjects received EVG/COBI/FTC/GS-7340 (150/150/200/40 or 150/150/200/25 mg), EVG/COBI/FTC/TDF (150/150/200/300 mg) or GS-7340 25 mg stand alone (SA), 12 days/treatment in a balanced Williams 4 x 4 design. In Study 2 (n=12), subjects sequentially received GS-7340 (8 mg) SA (Reference) for 12 days and GS-7340 plus COBI (8/150 mg) (Test) for 10 days. In Study 3 (n=34), across two cohorts (each 2 x 2 crossover design), subjects received EVG/COBI/FTC/GS-7340 (150/150/200/10 mg) (Test, both cohorts), EVG plus COBI (150/150 mg) (Reference, Cohort 1), and FTC plus GS-7340 (200/25 mg) (Reference, Cohort 2), each treatment dosed for 12 days. Statistical comparisons of GS-7340 and TFV were made using geometric mean ratios (GMR), with 90% confidence intervals (CI) of 70-143% (Study 1: Test = EVG/COBI/FTC/GS-7340, Reference = GS-7340 SA). Safety assessments were performed throughout dosing and follow up.

[0357] All treatments were generally well tolerated. Study 1 entailed 19/20 completers with one discontinuation from adverse events (AEs) (rhabdomyolysis (Grade 2) while receiving GS-7340 SA). All subjects completed Study 2, while 33 of 34 subjects completed Study 3. No Grade 3 or 4 AE was observed in the studies. In Study 1, when dosed as EVG/COBI/FTC/GS-7340, GS-7340 (25 mg) and resulting TFV exposures were substantially higher versus GS-7340 SA (GMR (90% CI) GS-7340 AUC_{last}: 222 (200, 246) and C_{max}: 223 (187, 265); TFV AUC_{tau}: 307 (290, 324), C_{max}: 368 (320, 423)). In Study 2, when dosed as GS-7340 plus COBI versus GS-7340 SA, GS-7340 exposures were similarly high, suggesting that the interaction observed in Study 1 was COBI-mediated (GMR (90% CI) GS-7340 AUC_{last}: 265 (229, 307) and C_{max}: 283 (220, 365, TFV AUC_{tau}: 331 (310, 353), C_{max}: 334 (302, 370), and C_{tau}: 335 (312, 359)). In Study 3, upon dose adjustment of GS-7340 to 10 mg, EVG/COBI/FTC/GS-7340 (150/150/200/10 mg) versus Reference resulted in comparable GS-7340 and TFV exposures. (GMR (90% CI) GS-7340 AUC_{last}: 89.0 (76.7, 103) and C_{max}: 97.3 (82.1, 115), TFV AUC_{last}: 124 (113, 136), C_{max}: 113 (98.8, 129), and C_{tau}: 120 (103, 140)).

EVG/COBI/FTC/GS-7340 STR provided similar EVG, COBI, and FTC exposures versus reference treatments and historical data.

[0358] GS-7340 and TFV exposures increase ~2-3 fold following coadministration with COBI or as EVG/COBI/FTC/GS-7340 dosing, which may be due to COBI inhibition of Pgp-mediated intestinal secretion of GS-7340. With a 10 mg dose of GS-7340, EVG/COBI/FTC/GS-7340 provided comparable GS-7340 and TFV exposures as GS-7340 at 25 mg and ~90% lower TFV exposure versus EVG/COBI/FTC/TDF.

Biological Example 6

[0359] EVG/COBI/FTC/TDF and EVG/COBI/FTC/tenofovir alafenamide hemifumarate were administered as single tablet regimens (STR) in a Phase 2 clinical trial evaluating safety and efficacy in HIV+ treatment-naïve adults. All subjects had HIV-1 RNA >5000 c/ml. Week 24 data indicated that treatment with the two STRs resulted in 87% of subjects on EVG/COBI/FTC/tenofovir alafenamide hemifumarate and 90% of subjects on EVG/COBI/FTC/TDF having HIV-1 RNA <50 c/ml. The EVG/COBI/FTC/tenofovir alafenamide hemifumarate STR was well tolerated, and relative to the known safety profile of EVG/COBI/FTC/TDF, no new or unexpected adverse drug reactions were identified.

[0360] Renal function was assessed in the subjects at week 24. When compared with subjects taking EVG/COBI/FTC/TDF, subjects taking EVG/COBI/FTC/ tenofovir alafenamide hemifumarate had significantly less reduction in the estimated glomerular filtration rate (eGFR), a trend towards less proteinuria, and statistically less tubular proteinuria. These differences may represent a reduction in subclinical tenofovir-associated nephrotoxicity.

[0361] To assess bone mineral density, dual-energy X-ray absorptiometry scans were performed at baseline and week 24. Subjects taking EVG/COBI/FTC/ tenofovir alafenamide hemifumarate experienced a significantly smaller reduction in bone mineral density at both spine and hip after 24 weeks, compared with subjects taking EVG/COBI/FTC/TDF. Importantly, the proportion of subjects with >3% decrease from baseline in hip bone mineral density was 10-fold lower in

the EVG/COBI/FTC/tenofovir alafenamide hemifumarate group than the EVG/COBI/FTC/TDF group (3.0% vs. 31.6%).

[0362] Together, these data support the hypothesis that TDF-associated renal and bone toxicity is driven by circulating tenofovir, as tenofovir levels are reduced by 90% in subjects administered EVG/COBI/FTC/tenofovir alafenamide hemifumarate.

[0363] All references, publications, patents, and patent documents cited herein are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

[0364] The use of the terms "a," "an," "the," and similar articles and the like in the context of describing the invention (including the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to"), unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein may be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention, unless otherwise claimed. No language in the specification should be construed as indicating any nonclaimed element as essential to the practice of the invention.

[0365] The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention. The skilled artisan recognizes that many other embodiments are

encompassed by the claimed invention and that it is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

WHAT IS CLAIMED IS:

1. A composition comprising: cobicistat, or a pharmaceutically acceptable salt thereof; and tenofovir alafenamide hemifumarate.

2. The composition of claim 1 comprising: 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof; and 3-40 mg of tenofovir alafenamide hemifumarate.

3. The composition of claim 1 or 2, further comprising a pharmaceutically acceptable carrier or diluent.

4. A method of treating a viral infection in a human comprising administering a composition of any one of claims 1-3 to the human.

5. A method of treating a viral infection in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, to the human.

6. A method of inhibiting activity of a retroviral reverse transcriptase comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate.

7. The method of claim 6, wherein the coadministering of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, is in a human.

8. Use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the prophylactic or therapeutic treatment of a viral infection in a human.

9. Use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for treating a viral infection in a human.

10. Use of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate, for the manufacture of a medicament for inhibiting activity of a retroviral reverse transcriptase.

11. The use of claim 10, wherein the medicament is for inhibiting activity of a retroviral reverse transcriptase in a human.

12. A method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising administering a composition of any one of claims 1-3 to the human.

13. A method of boosting an anti-viral effect of tenofovir alafenamide hemifumarate in a human comprising coadministering cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate to the human.

14. The method of claim 13, wherein 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

15. A method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human comprising administering a composition of any one of claims 1-3 to the human.

16. A method of inhibiting Pgp-mediated intestinal secretion of tenofovir alafenamide hemifumarate in a human by coadministration of cobicistat, or a pharmaceutically acceptable salt thereof, and tenofovir alafenamide hemifumarate.

17. The method of claim 16, wherein 50-500 mg of cobicistat, or a pharmaceutically acceptable salt thereof, is coadministered with 3-40 mg of tenofovir alafenamide hemifumarate.

18. The method of claim 4 or 5, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

19. The use of claim 8 or 9, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

20. The method of any one of claims 12-14, wherein the virus is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

21. A composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir.

22. A composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir.

23. A method of treating a viral infection in a human comprising administering a composition of claim 21 or 22 to the human.

24. A method of treating a viral infection in a human comprising coadministering (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir to the human.

25. The method of claim 24 comprising coadministering (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir to the human.

26. The use of the composition of claim 21 or 22 for the prophylactic or therapeutic treatment of a viral infection in a human.

27. Use of (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the manufacture of a medicament for treating a viral infection in a human.

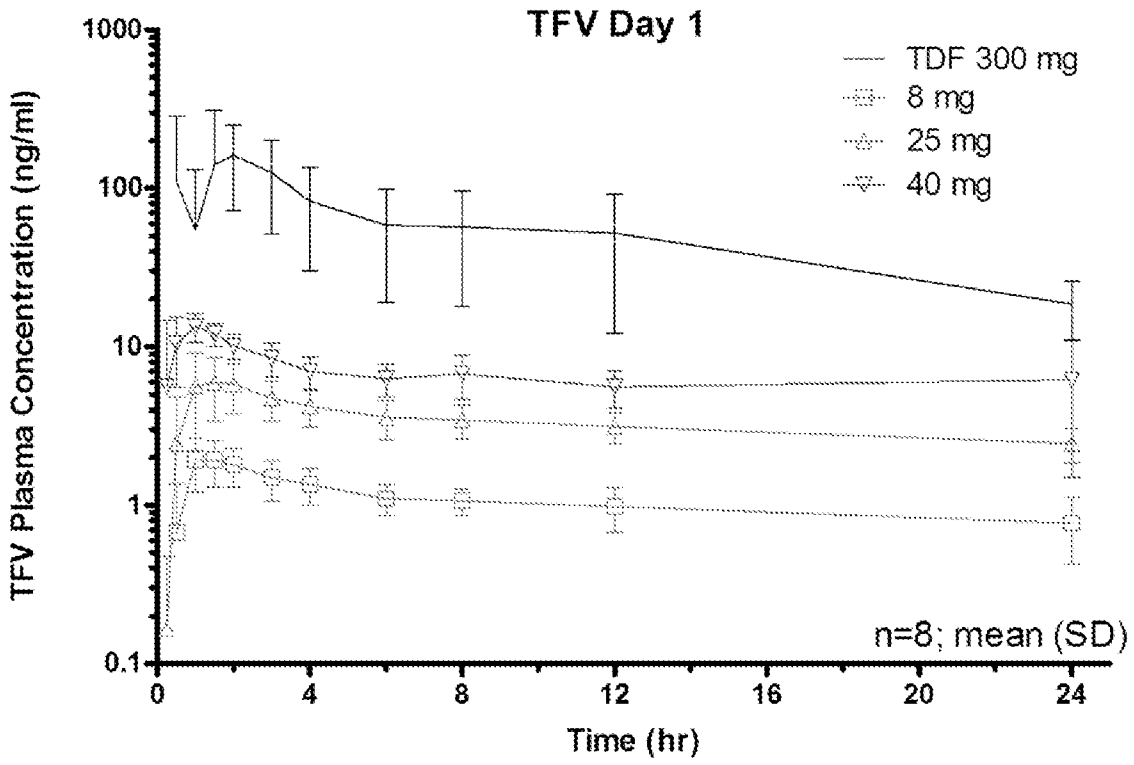
28. Use of (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the manufacture of a medicament for treating a viral infection in a human.

29. A composition comprising: (a) tenofovir alafenamide hemifumarate; (b) cobicistat, or a pharmaceutically acceptable salt thereof; (c) emtricitabine; and (d) elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

30. A composition comprising: (a) 3-40 mg tenofovir alafenamide hemifumarate; (b) 50-500 mg cobicistat, or a pharmaceutically acceptable salt thereof; (c) 50-500 mg emtricitabine; and (d) 50-500 mg elvitegravir for the treatment of a viral infection, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

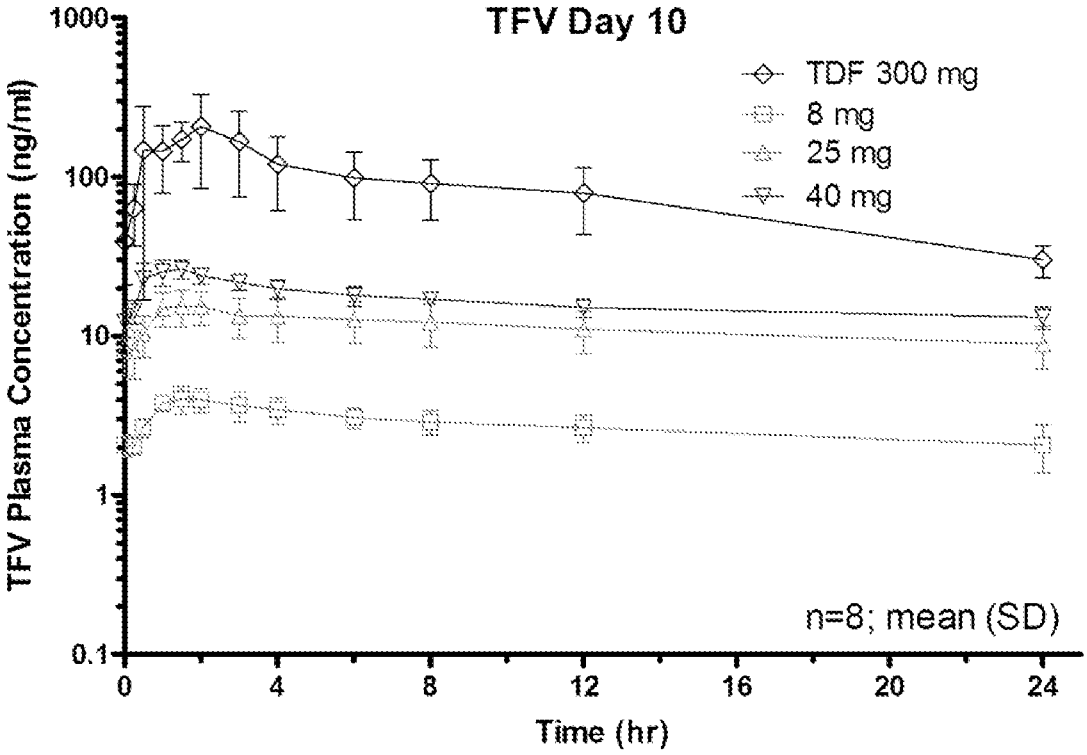
31. The method of any one of claims 23-25, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).

32. The use of any one of claims 26-28, wherein the viral infection is human immunodeficiency virus (HIV) or Hepatitis B virus (HBV).



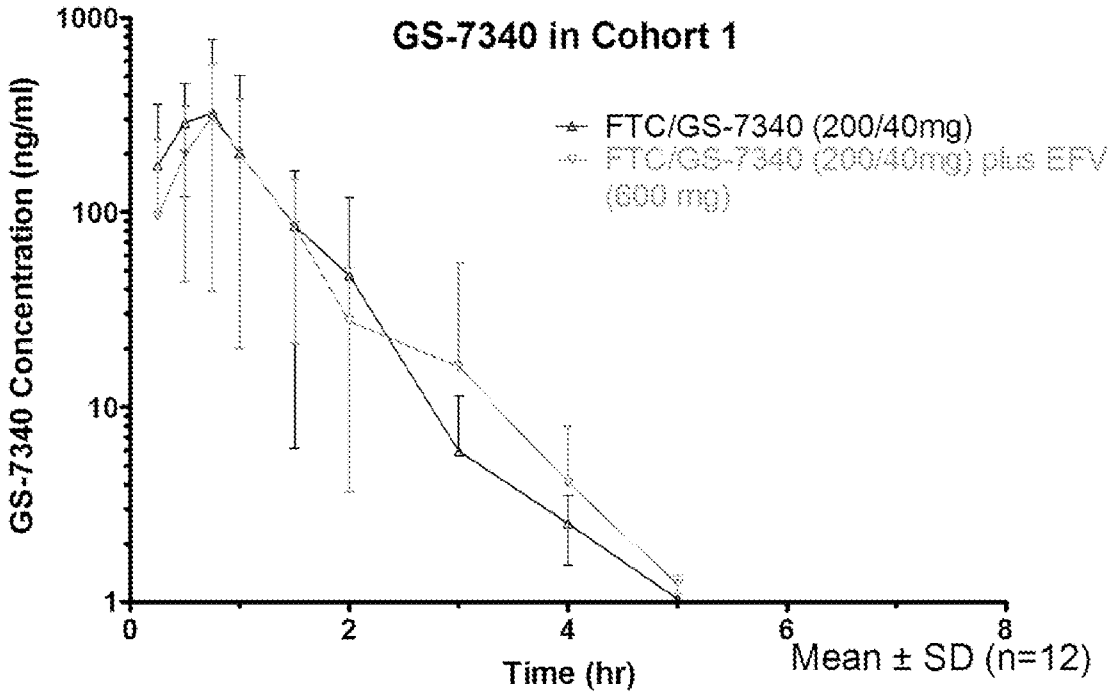
Day 1 PK Mean (%CV)	GS-7340 8 mg	GS-7340 25 mg	GS-7340 40 mg	TDF 300 mg
Cmax (ng/ml)	2 (30)	6.5 (40)	15 (36)	210 (52)
AUClast (ng.hr/ml)	25 (27)	70 (37)	143 (40)	1132 (48)

Figure 1



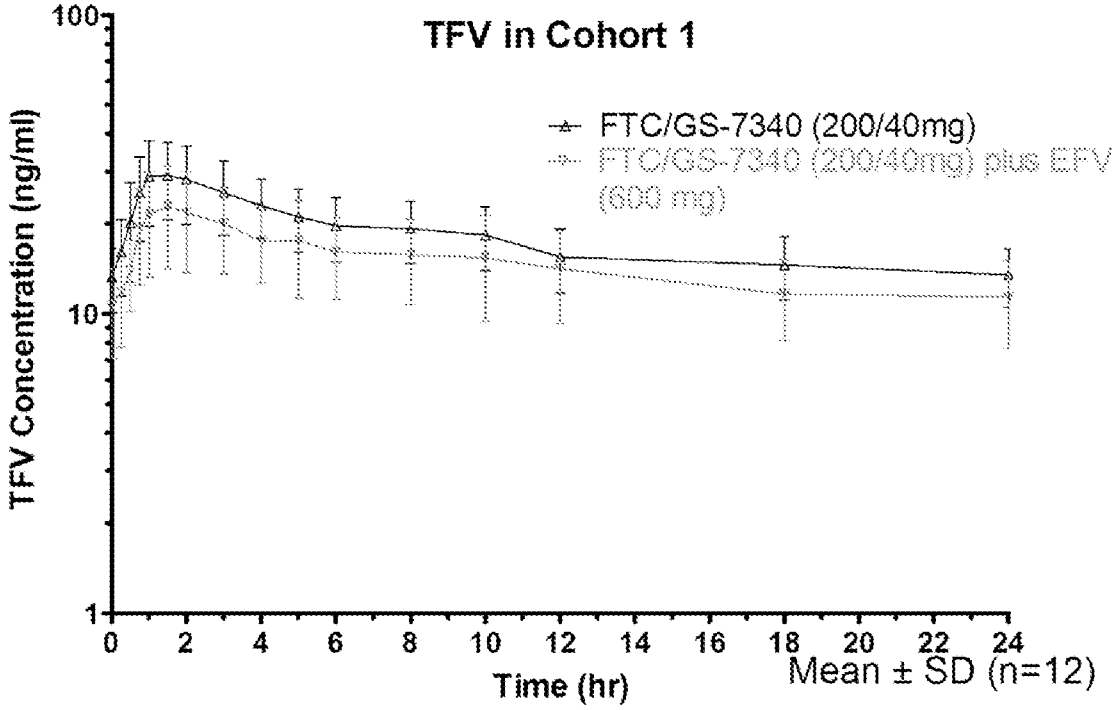
Day 10 PK Mean (%CV)	GS-7340 8 mg	GS-7340 25 mg	GS-7340 40 mg	TDF 300 mg
Cmax (ng/ml)	3.9 (28)	16 (22)	28 (9)	260 (43)
AUCtau (ng.hr/ml)	66 (19)	268 (29)	389 (11)	2090 (44)

Figure 2



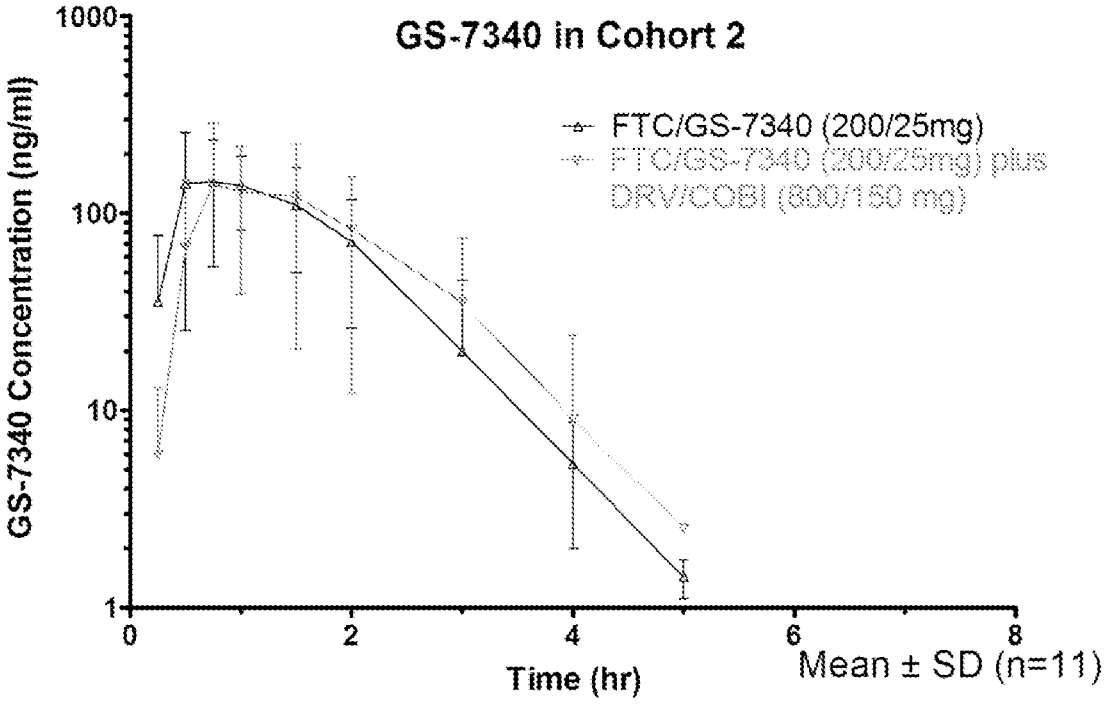
	GS-7340 PK in Cohort 1	
Mean (%CV)	FTC/GS-7340 (200/40 mg)	FTC/GS-7340 plus EFV 600 mg
AUC_{last} (ng.hr/ml)	330.5 (63)	285.5 (47)
C_{max} (ng/ml)	481.3 (83)	390.8 (62)

Figure 3A



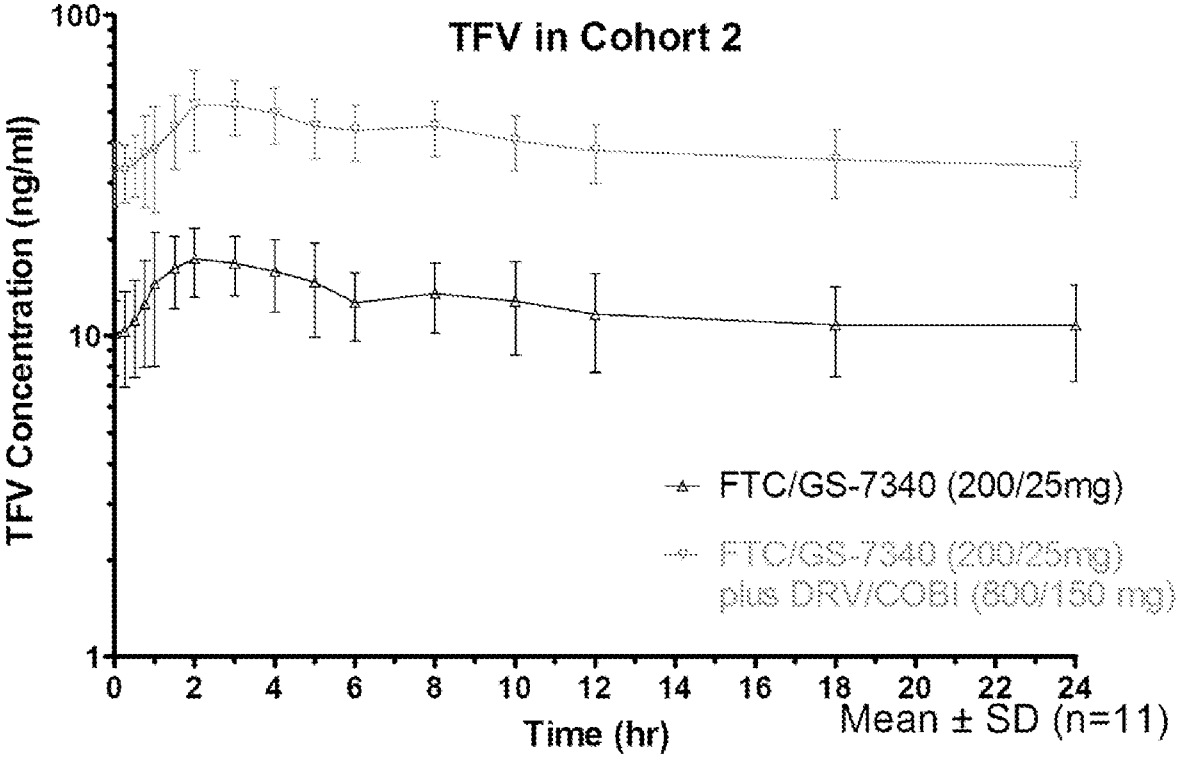
	TFV PK in Cohort 1	
Mean (%CV)	FTC/GS-7340 (200/40 mg)	FTC/GS-7340 plus EFV 600 mg
AUC_{0-24} (ng.hr/ml)	427.5 (23)	350.2 (32)
C_{max} (ng/ml)	31.4 (25)	24.0 (35)
C_{tau} (ng/ml)	13.5 (22)	11.3 (32)

Figure 3B



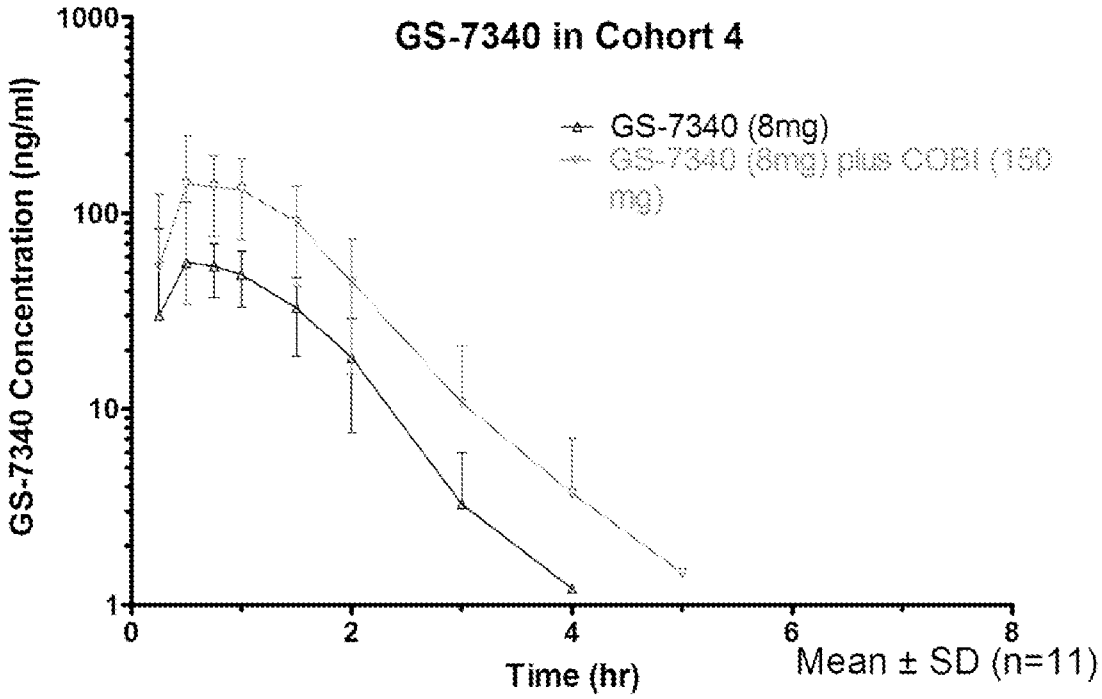
GS-7340 PK	Cohort 2		Cohort 3
Mean (%CV)	FTC/GS-7340 (200/25 mg)	FTC/GS-7340 plus DRV/COBI (800/150 mg)	FTC/GS-7340 (200/25 mg) plus DRV/COBI (800/150 mg)
AUC_{last} (ng.hr/ml)	245.6 (42)	243.9 (41)	271.0 (39)
C_{max} (ng/ml)	208.3 (40)	215.0 (59)	287.4 (73)

Figure 4A



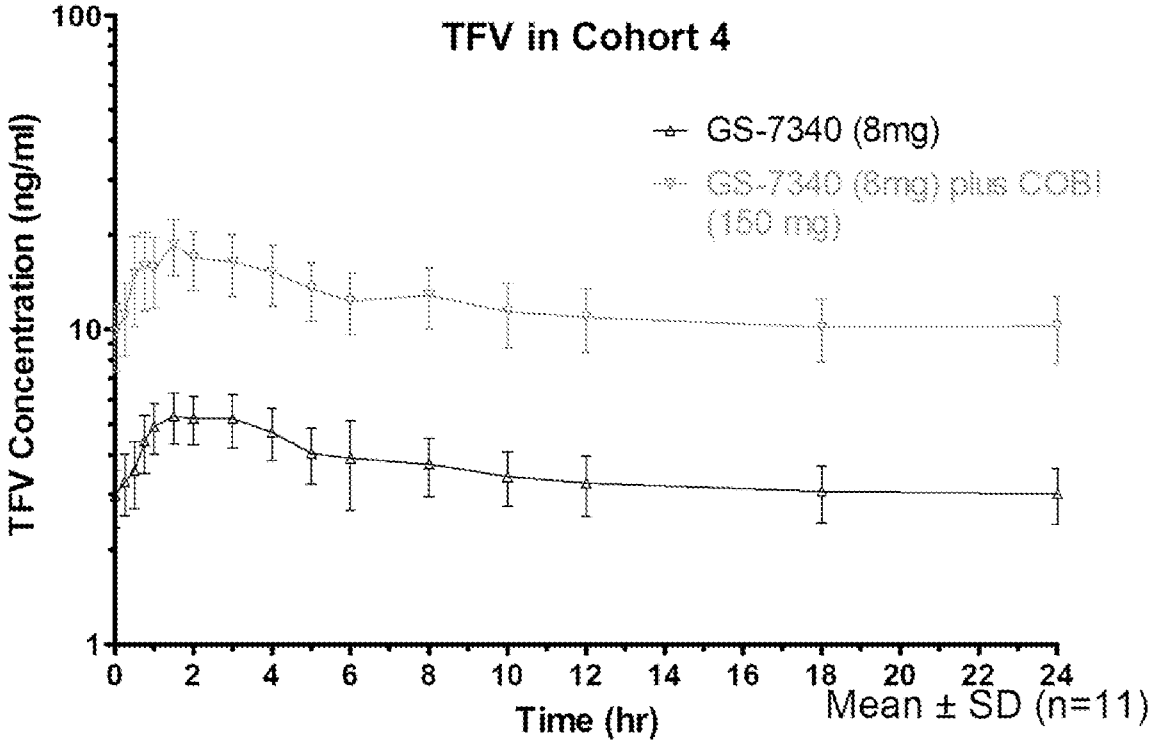
TFV PK	Cohort 2		Cohort 3
Mean (%CV)	FTC/GS-7340 (200/25 mg)	FTC/GS-7340 plus DRV/COBI (800/150 mg)	FTC/GS-7340 (200/25 mg) plus DRV/COBI (800/150 mg)
AUC_{tau} (ng.hr/ml)	299.2 (29)	953.4 (20)	967.6 (13)
C_{max} (ng/ml)	18.3 (28)	57.4 (23.2)	57.7 (15)
C_{tau} (ng/ml)	10.8 (33)	33.7 (20)	36.2 (13)

Figure 4B



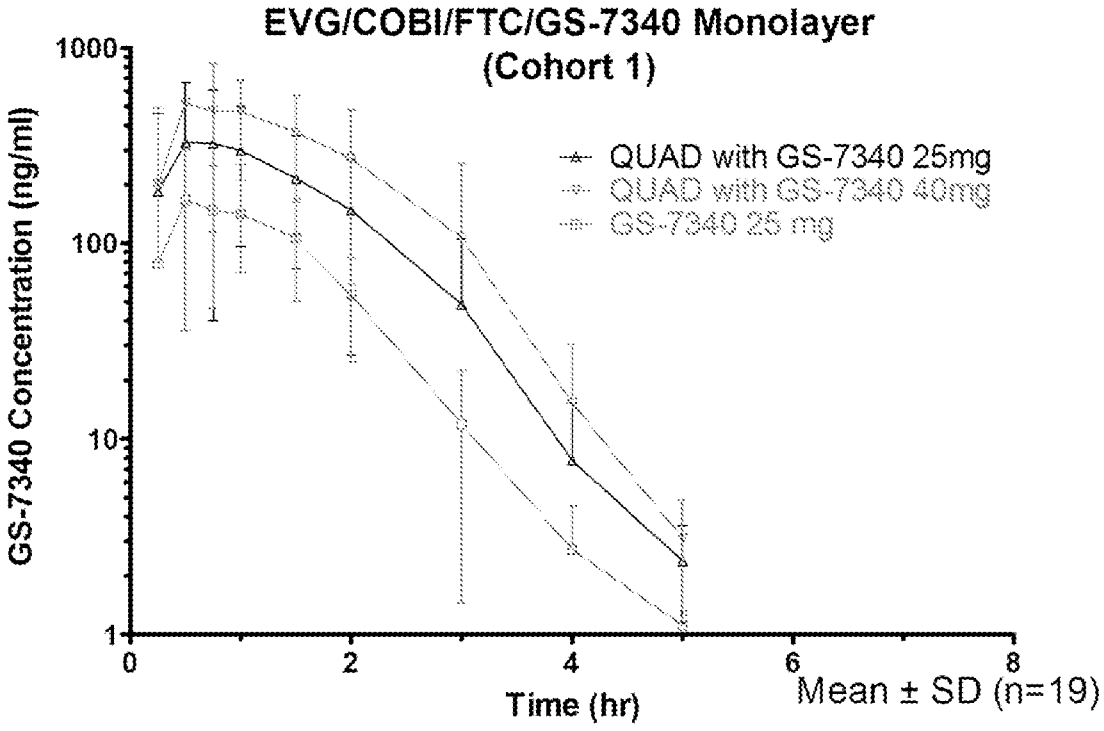
	Cohort 4			
	Steady State PK		Single Dose PK	
Mean (%CV)	GS-7340 (8 mg)	GS-7340 (8 mg) plus COBI (150 mg)	GS-7340 (8 mg)	GS-7340 (8 mg) plus COBI (150 mg)
AUC_{last} (ng.hr/ml)	81.2 (44)	213.3 (38)	64.7 (34)	188.0 (27)
C_{max} (ng/ml)	71.0 (73)	189.9 (46)	49.9 (38)	141.5 (33)

Figure 5A



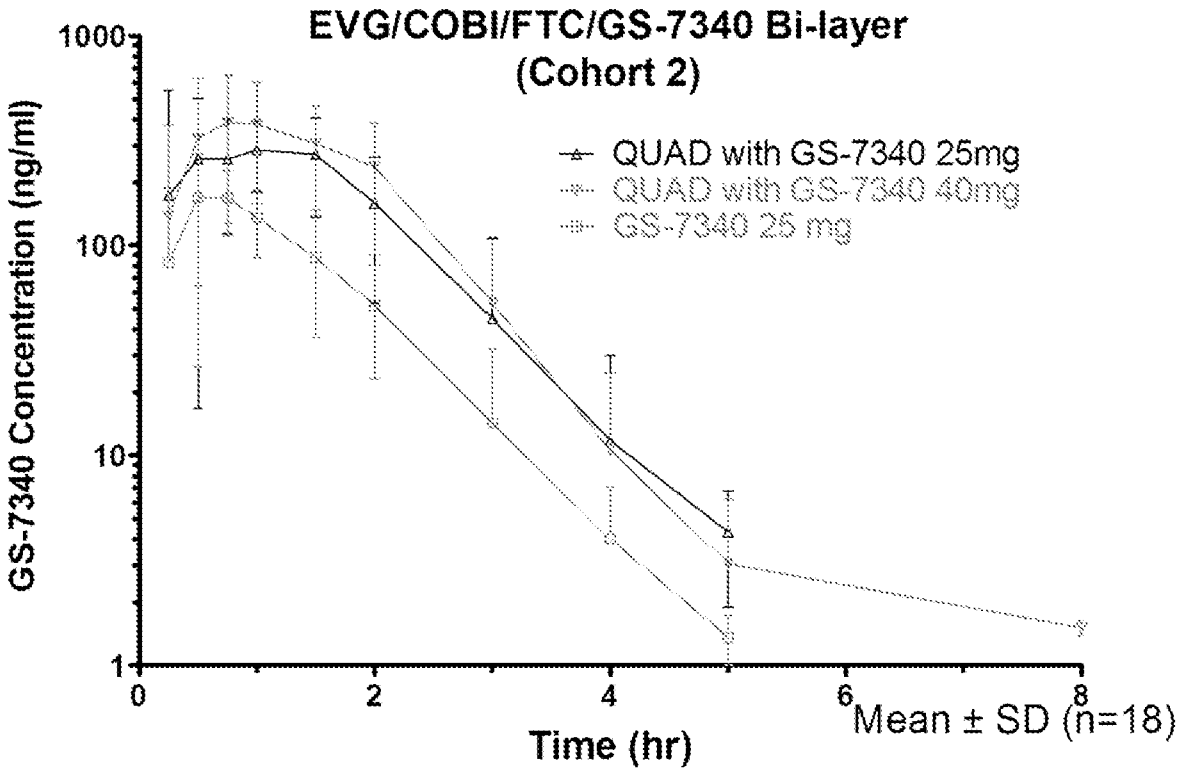
	TFV PK Multiple Dose PK	
Mean (%CV)	GS-7340 (8 mg)	GS-7340 (8 mg) plus COBI (150 mg)
AUC_{tau} (ng.hr/ml)	86.1 (19)	286.9 (22)
C_{max} (ng/ml)	5.8 (19)	19.3 (20)
C_{tau} (ng/ml)	3.0 (20)	10.2 (24)

Figure 5B



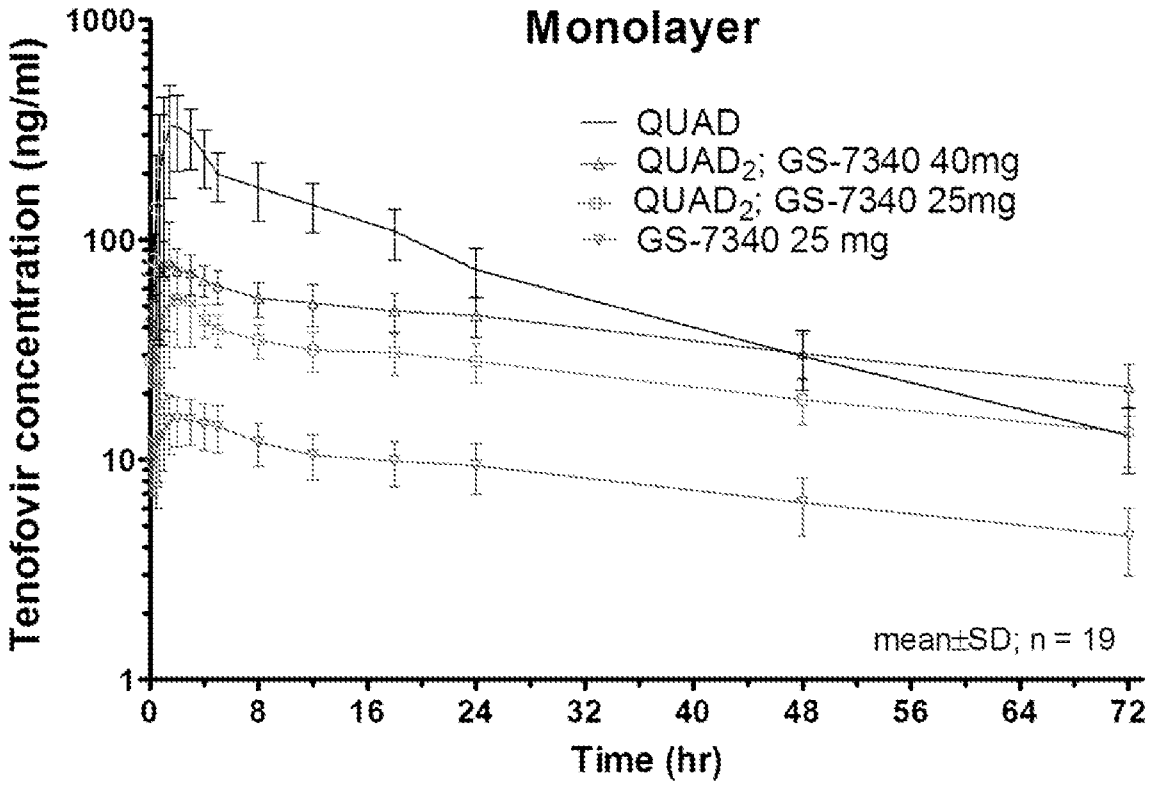
Monolayer Mean (%CV)	$QUAD_2$ with GS-7340 25 mg	$QUAD_2$ with GS-7340 40 mg	GS-7340 25 mg
C_{max} (ng/ml)	506 (54)	793 (52)	215 (55)
AUC_{tau} (ng.hr/ml)	552 (41)	929 (34)	243 (42)

Figure 6



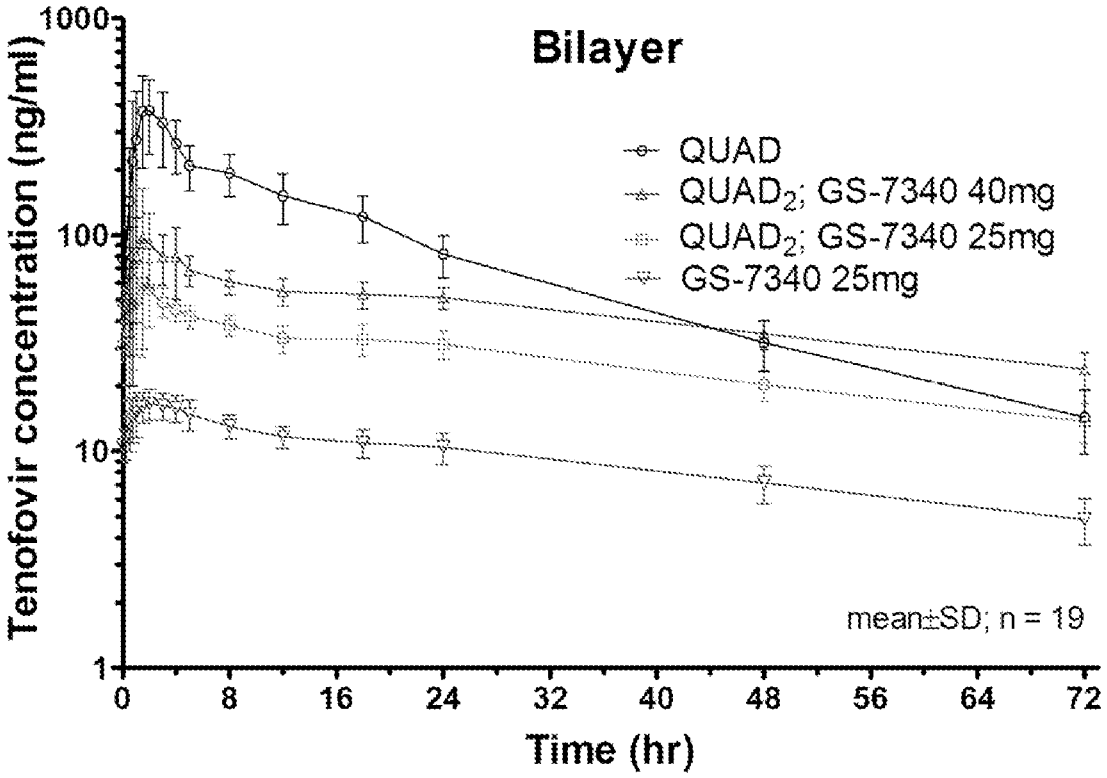
Bi-layer Mean (%CV)	$QUAD_2$ with GS-7340 25 mg	$QUAD_2$ with GS-7340 40 mg	GS-7340 25 mg
C_{max} (ng/ml)	472 (58)	587 (33)	211 (44)
AUC_{tau} (ng.hr/ml)	559 (29)	760 (27)	245 (34)

Figure 7



Monolayer Mean (%CV)	$QUAD_2$ 25 mg	$QUAD_2$ 40 mg	GS-7340 25 mg	QUAD
C_{max} (ng/ml)	66 (51)	103 (64)	16 (25)	445 (29)
C_{tau} (ng/ml)	28.1 (20)	45.4 (21)	9.40 (26)	73.1 (25)
AUC_{tau} (ng.hr/ml)	837 (18)	1310 (21)	274 (24)	3760 (22)

Figure 8



Bi-layer Mean (%CV)	$QUAD_2$ 25 mg	$QUAD_2$ 40 mg	GS-7340 25 mg	QUAD
C_{max} (ng/ml)	71.9 (57)	117 (60)	17.5 (15)	505 (27)
C_{tau} (ng/ml)	31.3 (15)	51.4 (12)	10.5 (17)	81.6 (22)
AUC_{tau} (ng.hr/ml)	899 (13)	1460 (16)	301 (13)	4120 (22)

Figure 9

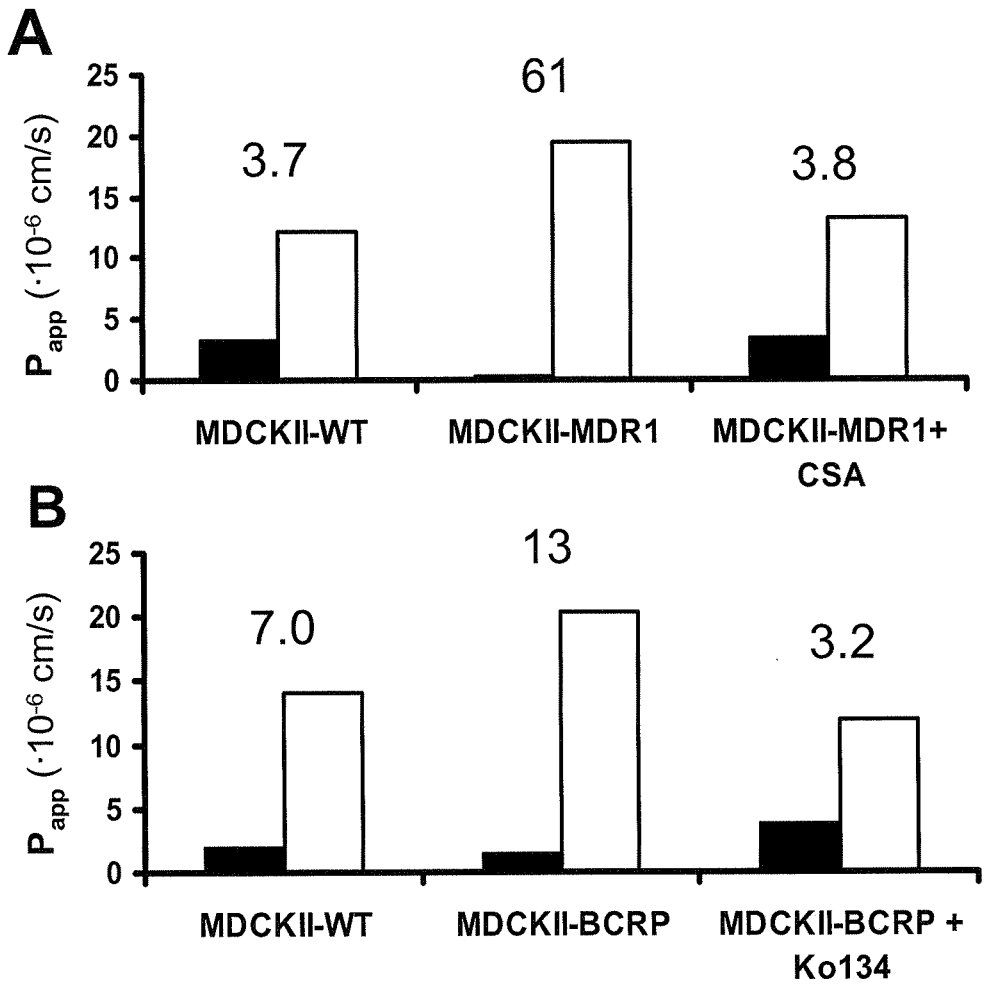

A
25
20
15
10
5
0
P_{app} ($\cdot 10^{-6}$ cm/s)
3.7
61
3.8
MDCKII-WT
MDCKII-MDR1
MDCKII-MDR1+ CSA
B
25
20
15
10
5
0
P_{app} ($\cdot 10^{-6}$ cm/s)
7.0
13
3.2
MDCKII-WT
MDCKII-BCRP
MDCKII-BCRP + Ko134

Figure 10

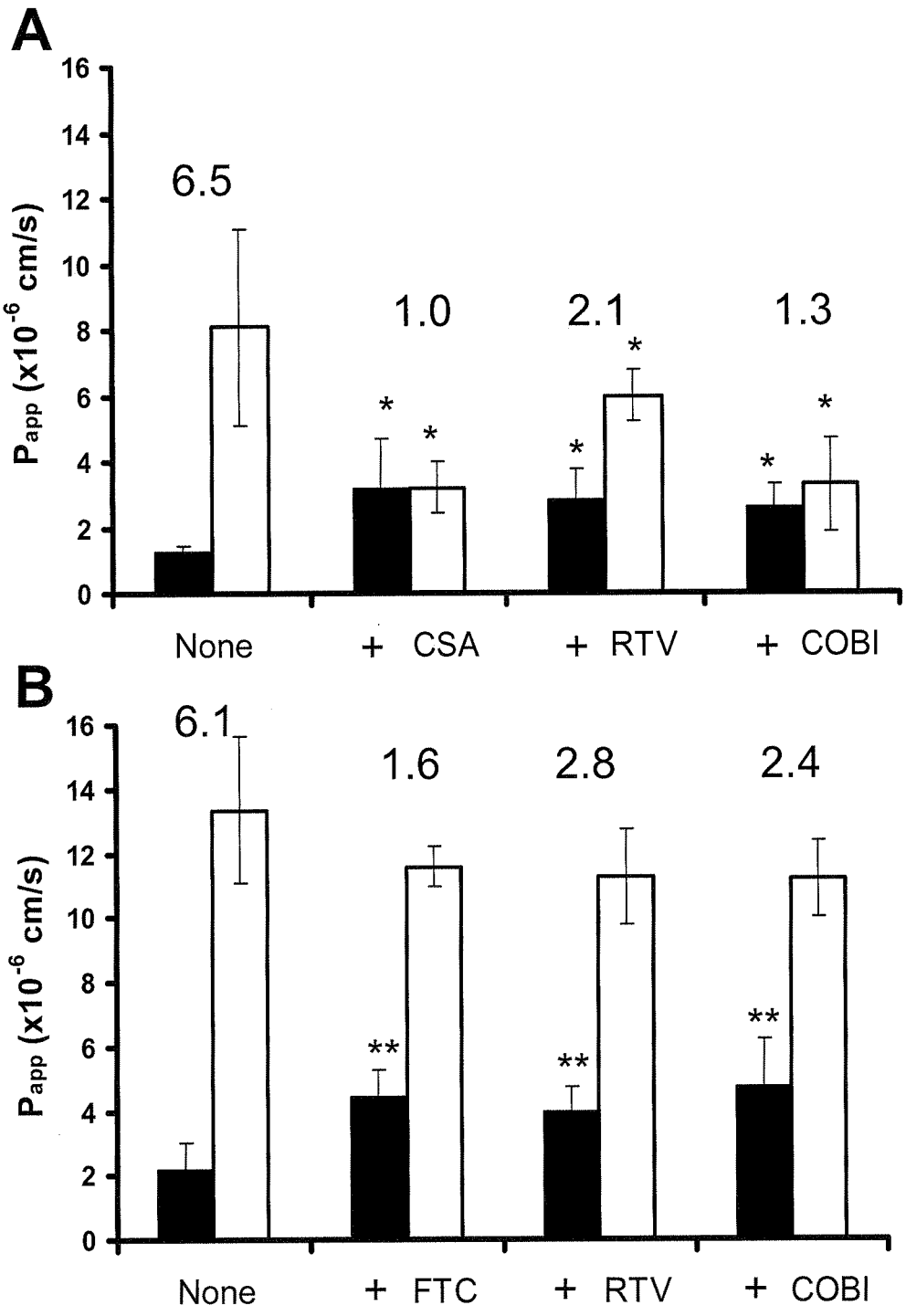

A
16
14
12
10
8
6
4
2
0
P_{app} ($x10^{-6}$ cm/s)
6.5
1.0
2.1
1.3
*
None
+ CSA
+ RTV
+ COBI
B
6.1
1.6
2.8
2.4
**
None
+ FTC
+ RTV
+ COBI

Figure 11

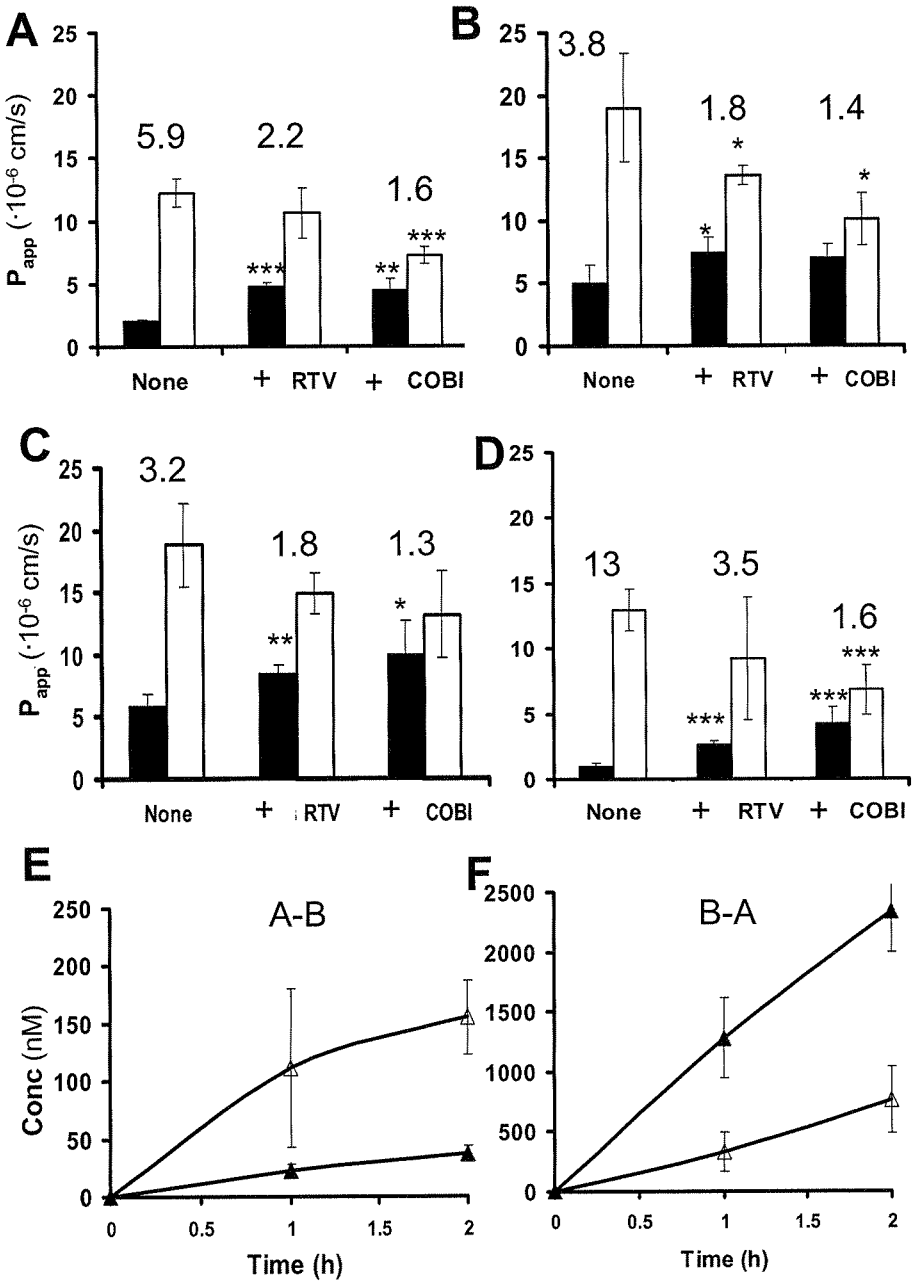

A
B
C
D
E
F
P_{app} ($\cdot 10^{-6}$ cm/s)
5.9
2.2
1.6
3.8
1.8
1.4
3.2
1.8
1.3
13
3.5
1.6
None
+ RTV
+ COBI
A-B
B-A
Conc (nM)
Time (h)

Figure 12

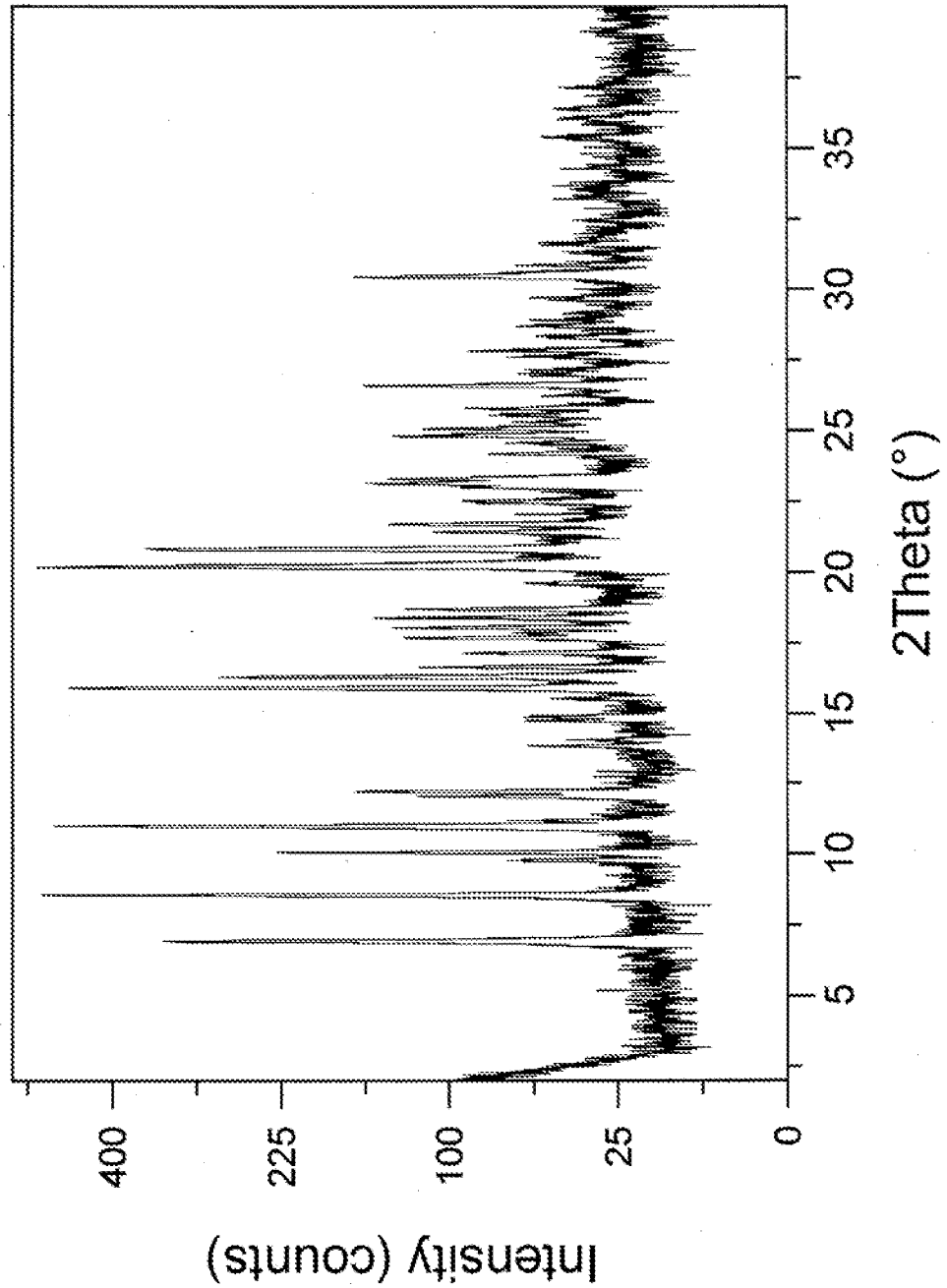


Figure 13

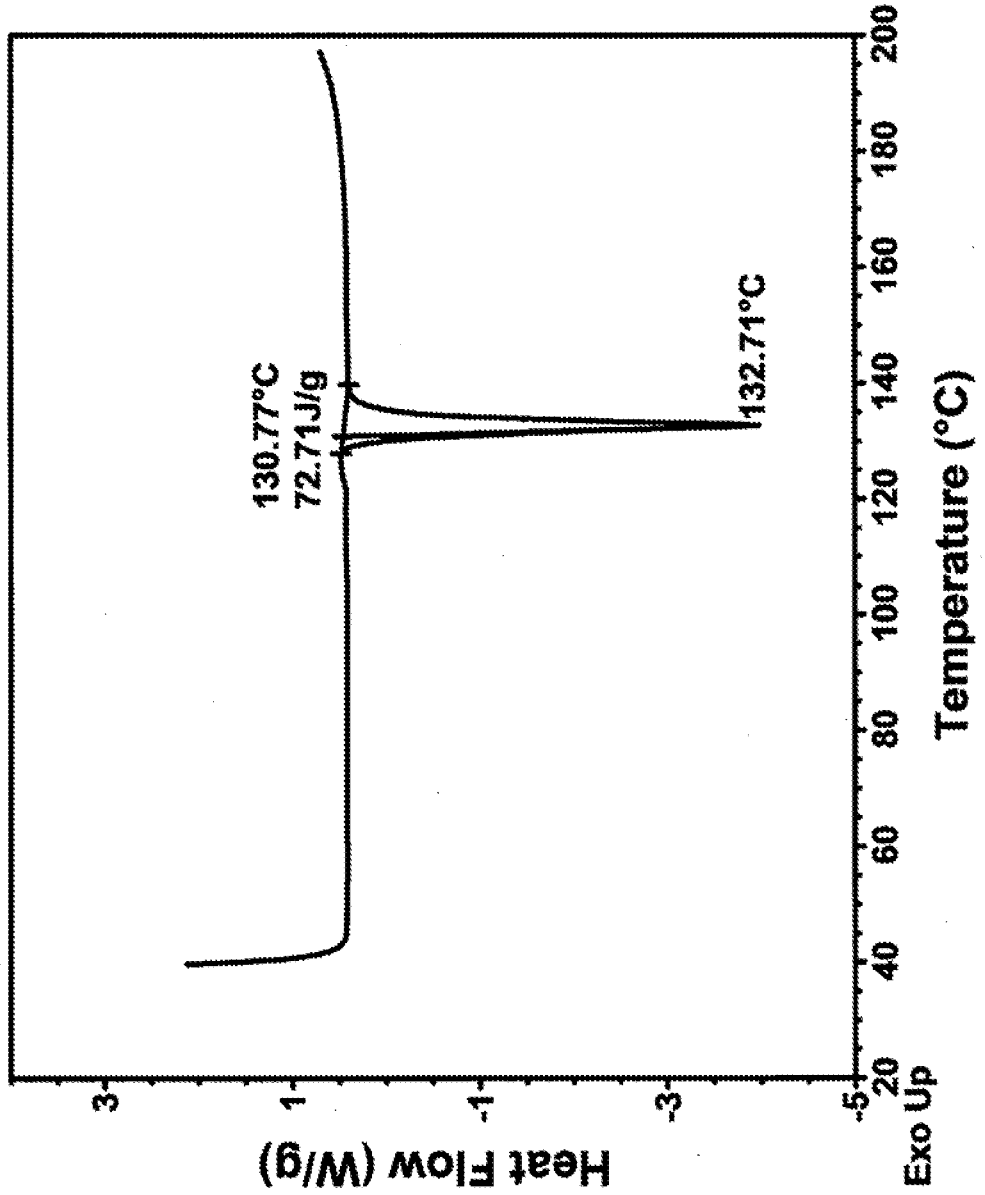

130.77°C
72.71J/g
132.71°C
Heat Flow (W/g)
Exo Up
Temperature (°C)
3
1
-1
-3
-5
20
40
60
80
100
120
140
160
180
200

Figure 14

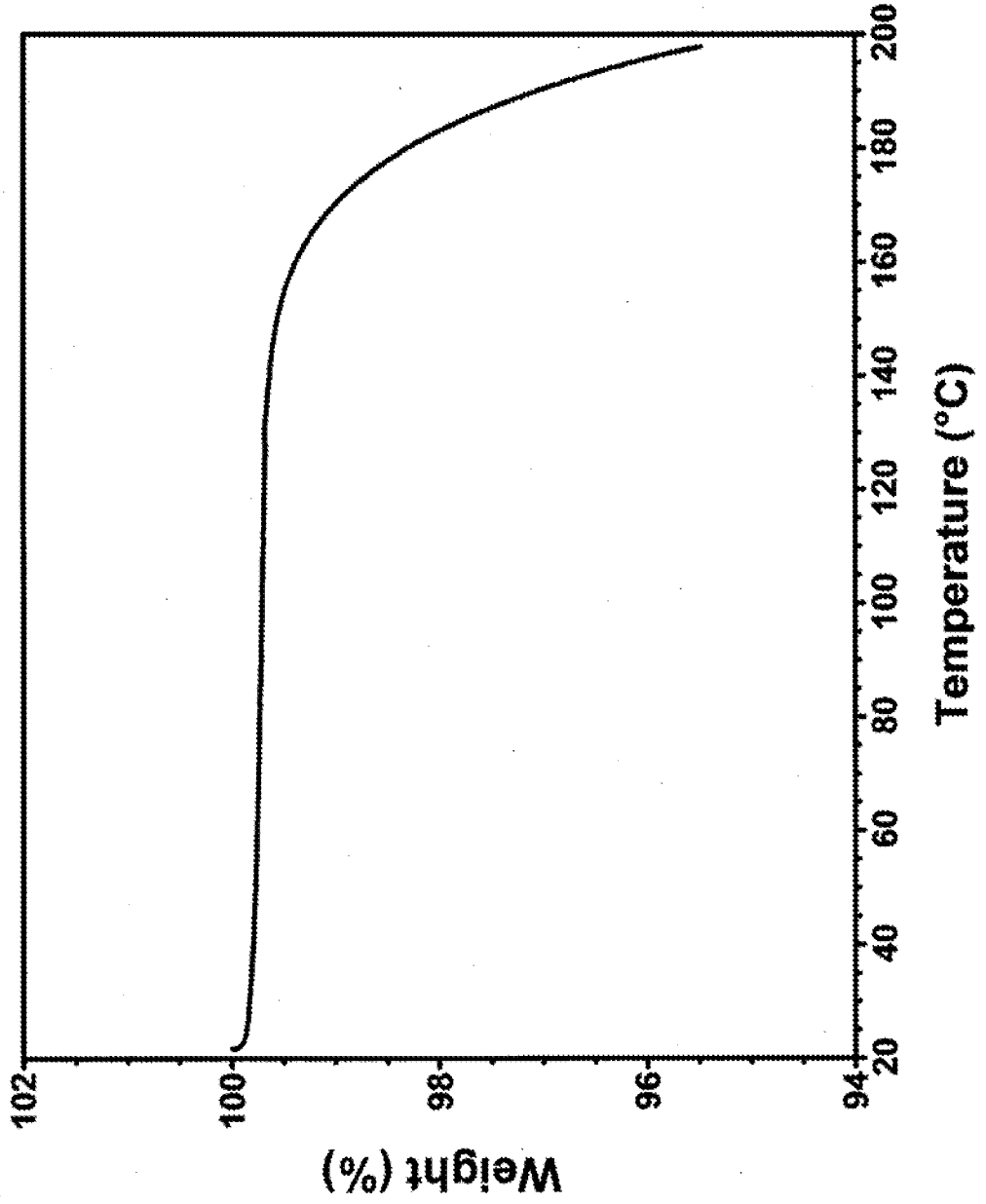

Weight (%)
102
100
98
96
94
Temperature (°C)
20
40
60
80
100
120
140
160
180
200

Figure 15

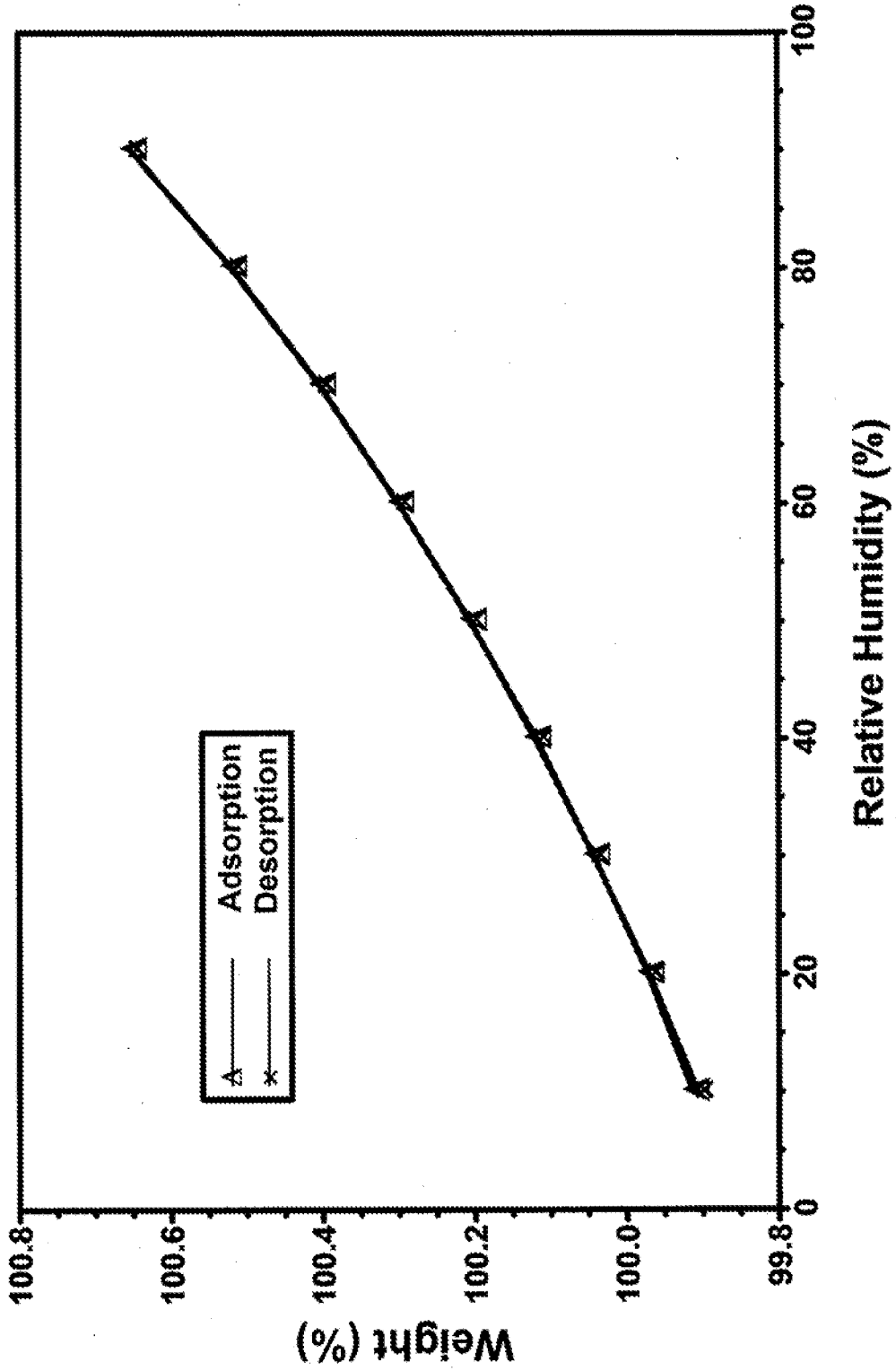

Weight (%)
100.8
100.6
100.4
100.2
100.0
99.8
0
20
40
60
80
100
Relative Humidity (%)
Adsorption
Desorption

Figure 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/024438

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/513 A61K31/5377 A61K31/675 A61K31/47 A61P31/12
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"GS-7340", Thomson Reuters Drug News, 2002, XP002694095, Retrieved from the Internet: URL:http://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_llista t_refs?p_session_id=2207762&p_orig=&p_coun t=45&p_ [retrieved on 2013-01-29] the whole document ----- -/--	1-32

[X] Further documents are listed in the continuation of Box C.

[X] 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
19 March 2013	16/04/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Renard, Delphine

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/024438

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	"Phase II trial investigates GS-7340 as part of a new treatment regimen", Thomson Reuters Drug News, 26 January 2012 (2012-01-26), XP055051645, Retrieved from the Internet: URL:http://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_related_ref_to?p_id=315936&p_origen=PRO&p_tsearch=#link [retrieved on 2013-01-29] "phase IIa studies ....10 times lower than than that of Viread" "once daily tablet containing GS-7340 (10 mg), cobicistat (150 mg), elvitegravir (150 mg) and emtricitabine (200 mg)"	1-32
A	WO 2010/091197 A2 (GILEAD SCIENCES INC [US]; OLIYAI REZA [US]; MENNING MARK M [US]; KOZIA) 12 August 2010 (2010-08-12) claims 1, 6; examples 1-4	1-12
A	RICHARD ELION ET AL: "Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection", AIDS, vol. 25, no. 15, 1 September 2011 (2011-09-01), pages 1881-1886, XP055051636, ISSN: 0269-9370, DOI: 10.1097/QAD.0b013e32834b4d48 abstract the whole document	1-12
X,P	Liz Highleyman: "ICAAC 2012: New Tenofovir Pro-drug Matches Potency of Original Version but with Less Toxicity", hivandhepatitis.com, 6 December 2012 (2012-12-06), XP055052016, Retrieved from the Internet: URL:http://www.hivandhepatitis.com/hiv-aids/hiv-aids-topics/hiv-treatment/3853-new-tenofovir-pro-drug-matches-potency-of-original-version-but-with-less-toxicity [retrieved on 2013-02-01] the whole document	1-32

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/024438

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	LEPIST EI ET AL: "Cobicistat Boosts the Intestinal Absorption of Transport Substrates, Including HIV Protease Inhibitors and GS-7340, In Vitro", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US, vol. 56, no. 10, 1 October 2012 (2012-10-01), pages 5409-5413, XP009166632, ISSN: 0066-4804 the whole document	1-32
E	WO 2013/025788 A1 (GILEAD SCIENCES INC [US]; LIU DAZHAN [CA]; SHI BING [US]; WANG FANG [U) 21 February 2013 (2013-02-21) claims 1,14,17; tables 2-3	1-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/024438

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010091197 A2	12-08-2010	AR 075369 A1	30-03-2011
		AU 2010210598 A1	25-08-2011
		CA 2750521 A1	12-08-2010
		CN 102307573 A	04-01-2012
		EA 201190125 A1	30-01-2012
		EC SP11011307 A	31-10-2011
		EP 2393485 A2	14-12-2011
		JP 2012517432 A	02-08-2012
		KR 20110122729 A	10-11-2011
		PE 09942011 A1	24-01-2012
		SG 173544 A1	29-09-2011
		TW 201040142 A	16-11-2010
		US 2010285122 A1	11-11-2010
		UY 32424 A	30-09-2010
		WO 2010091197 A2	12-08-2010
WO 2013025788 A1	21-02-2013	US 2013065856 A1	14-03-2013
		WO 2013025788 A1	21-02-2013

(19)中华人民共和国国家知识产权局

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61/624,676 2012.04.16 US
61/692,392 2012.08.23 US
61/737,493 2012.12.14 US

(85)PCT国际申请进入国家阶段日
2014.08.01

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(71)申请人 吉联亚科学公司
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(74)专利代理机构 北京律盟知识产权代理有限责任公司 11287
代理人 江葳

(51)Int.Cl.
A61K 31/513(2006.01)
A61K 31/5377(2006.01)
A61K 31/675(2006.01)
A61K 31/47(2006.01)
A61P 31/12(2006.01)

权利要求书2页 说明书49页 附图19页

(54)发明名称

用于治疗病毒感染的包含替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他的组合疗法

(57)摘要

本发明公开{9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}的半反丁烯二酸盐形式(替诺福韦艾拉酚胺半反丁烯二酸盐)与可比西他组合的用途。另外,公开替诺福韦艾拉酚胺半反丁烯二酸盐、可比西他、恩曲他滨和埃替格韦的组合以及替诺福韦艾拉酚胺半反丁烯二酸盐、可比西他、恩曲他滨和地瑞那韦的组合。

CN 104105484 A

1. 一种组合物，其包含：可比西他或其医药学上可接受的盐；和替诺福韦艾拉酚胺半反丁烯二酸盐。

2. 根据权利要求 1 所述的组合物，其包含：50-500mg 可比西他或其医药学上可接受的盐；和 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐。

3. 根据权利要求 1 或 2 所述的组合物，其进一步包含医药学上可接受的载剂或稀释剂。

4. 一种治疗人的病毒感染的方法，其包含向所述人投与根据权利要求 1 到 3 中任一权利要求所述的组合物。

5. 一种治疗人的病毒感染的方法，其包含向所述人共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐。

6. 一种抑制逆转录病毒逆转录酶的活性的方法，其包含共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐。

7. 根据权利要求 6 所述的方法，其中所述可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的共投与是在人中。

8. 一种可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的用途，其用于防治性或治疗性治疗人的病毒感染。

9. 一种可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的用途，其用于制造供治疗人的病毒感染用的药物。

10. 一种可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的用途，其用于制造供抑制逆转录病毒逆转录酶活性用的药物。

11. 根据权利要求 10 所述的用途，其中所述药物是用于抑制人的逆转录病毒逆转录酶活性。

12. 一种在人中增强替诺福韦艾拉酚胺半反丁烯二酸盐的抗病毒作用的方法，其包含向所述人投与根据权利要求 1 到 3 中任一权利要求所述的组合物。

13. 一种在人中增强替诺福韦艾拉酚胺半反丁烯二酸盐的抗病毒作用的方法，其包含向所述人共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐。

14. 根据权利要求 13 所述的方法，其中 50-500mg 可比西他或其医药学上可接受的盐是与 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐共投与的。

15. 一种在人中抑制替诺福韦艾拉酚胺半反丁烯二酸盐的 Pgp 介导的肠道分泌的方法，其包含向所述人投与根据权利要求 1 到 3 中任一权利要求所述的组合物。

16. 一种在人中抑制替诺福韦艾拉酚胺半反丁烯二酸盐的 Pgp 介导的肠道分泌的方法，其通过共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐进行。

17. 根据权利要求 16 所述的方法，其中 50-500mg 可比西他或其医药学上可接受的盐是与 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐共投与的。

18. 根据权利要求 4 或 5 所述的方法，其中所述病毒感染是人类免疫缺陷病毒 HIV 或乙型肝炎病毒 HBV。

19. 根据权利要求 8 或 9 所述的用途，其中所述病毒感染是人类免疫缺陷病毒 HIV 或乙型肝炎病毒 HBV。

20. 根据权利要求 12 到 14 中任一权利要求所述的方法，其中所述病毒是人类免疫缺陷

病毒 HIV 或乙型肝炎病毒 HBV。

21. 一种组合物，其包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦。

22. 一种组合物，其包含：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦。

23. 一种治疗人的病毒感染的方法，其包含向所述人投与根据权利要求 21 或 22 所述的组合物。

24. 一种治疗人的病毒感染的方法，其包含向所述人共投与 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦。

25. 根据权利要求 24 所述的方法，其包含向所述人共投与 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦。

26. 一种根据权利要求 21 或 22 所述的组合物的用途，其用于防治性或治疗性治疗人的病毒感染。

27. 一种 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦的用途，其用于制造供治疗人的病毒感染用的药物。

28. 一种 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦的用途，其用于制造供治疗人的病毒感染用的药物。

29. 一种组合物，其包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 HIV 或乙型肝炎病毒 HBV。

30. 一种组合物，其包含：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 HIV 或乙型肝炎病毒 HBV。

31. 根据权利要求 23 到 25 中任一权利要求所述的方法，其中所述病毒感染是人类免疫缺陷病毒 HIV 或乙型肝炎病毒 HBV。

32. 根据权利要求 26 到 28 中任一权利要求所述的用途，其中所述病毒感染是人类免疫缺陷病毒 HIV 或乙型肝炎病毒 HBV。

用于治疗病毒感染的包含替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他的组合疗法

[0001] 相关申请案的交叉参考

[0002] 本申请案要求以下各项的优先权：2012 年 2 月 3 日提交的美国临时专利申请案第 61/594,894 号；2012 年 3 月 30 日提交的美国临时专利申请案第 61/618,411 号；2012 年 4 月 16 日提交的美国临时专利申请案第 61/624,676 号；2012 年 8 月 23 日提交的美国临时专利申请案第 61/692,392 号；和 2012 年 12 月 14 日提交的美国临时专利申请案第 61/737,493 号，所述申请案各自的内容特此以全文引用的方式并入本文中。

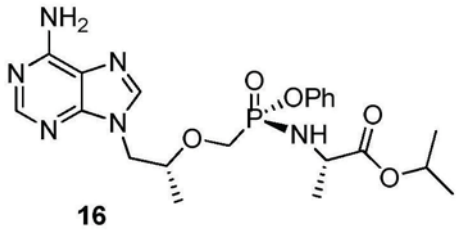
背景技术

[0003] 替诺福韦 (tenofovir){9-R-[(2- 膦酰甲氧基) 丙基] 腺嘌呤 }(一种 dAMP 的非环核苷酸类似物) 是人类免疫缺陷病毒 1 型 (HIV-1) 复制的强力体外和体内抑制剂。替诺福韦在细胞中依序被 AMP 激酶和核苷二磷酸激酶磷酸化成活性物质 (替诺福韦二磷酸酯), 所述活性物质充当终止生长病毒 DNA 链的 HIV-1 逆转录酶的竞争性抑制剂。替诺福韦中存在非水解膦酸部分避免了对于 HIV 逆转录酶的核苷类似物抑制剂的激活可具速率限制性的初始磷酸化步骤。由于存在膦酸酯基团，故替诺福韦在中性 pH 值下是带负电荷的，由此限制其口服生物利用度。

[0004] 第一代口服替诺福韦前药反丁烯二酸替诺福韦酯 (Tenofovir disoproxil fumarate，TDF；VIREAD®) 已在临床试验中得到广泛研究，且已在许多国家获得上市许可，作为与其它抗逆转录病毒剂结合的每日一次片剂 (300mg) 用于治疗 HIV-1 感染。

[0005] 美国专利第 7,390,791 号描述了适用于疗法的某些膦酸酯核苷酸类似物前药。一种所述前药是 9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基) 乙基] 氨基] 苯氧基氧膦基]- 甲氧基] 丙基] 腺嘌呤 16：

[0006]



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[0007] GS-7340{9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基) 乙基] 氨基] 苯氧基氧膦基] 甲氧基] 丙基] 腺嘌呤 } 是替诺福韦 (9-[(2- 膦酰甲氧基) 丙基] 腺嘌呤) 的异丙基丙氨酸基苯酯前药。GS-7340 相对于替诺福韦展示出强力抗 HIV 活性 500 到 1000 倍增强的活性对抗 T 细胞、激活的外周血液单核淋巴细胞 (PBMC) 和巨噬细胞中的 HIV-1。GS-7340 还具有增强的在体内将母体替诺福韦传递到 PBMC 和其它淋巴组织中并增加母体替诺福韦累积的能力。其还是乙型肝炎病毒的强力抑制剂。

[0008] GS-7340 被代谢成替诺福韦，其在转化成活性代谢物二磷酸替诺福韦 (PMPApp) 的第一步骤中并不依赖于细胞内核苷激酶活性。负责将替诺福韦代谢成活性二磷酸化形式的

细胞酶是高活性且普遍存在的腺苷酸激酶和核苷酸二磷酸激酶。腺苷酸激酶以多种同工酶(AK1 到 AK4) 形式存在,其中替诺福韦的磷酸化由 AK2 最有效地介导。

[0009] 替诺福韦并不在人体外或体内作为底物、抑制剂或诱导剂与人类药物代谢细胞色素 P450 酶或 UDP- 葡萄糖醛酸转移酶显著互相作用。GS-7340 具备有限的经由抑制改变细胞色素 P450 酶活性的潜力 (与所有所测试的同工型比较,IC_{50} ＞ 7μM)。类似地,GS-7340 并不在高达 50μM 的浓度下抑制 UGT1A1 功能。另外,GS-7340 并不是芳基烃受体或人类孕烷 X 受体的激活剂。

[0010] 尽管替诺福韦和 GS-7340 展示出所需活性,但处理成本和不当副作用的可能性均可随着所需药物剂量增加而增加。因此,需要适用于使用减小剂量的替诺福韦或 GS-7340 实现可接受的抗病毒作用的方法和组合物。

[0011] 美国专利第 7,390,791 号和美国专利第 7,803,788 号 (其各自的内容以全文引用的方式并入本文中) 还描述了适用于疗法的某些膦酸酯核苷酸类似物前药。如上所述,一种所述前药是 9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基) 乙基] 氨基] 苯氧基氧膦基] 甲氧基] 丙基] 腺嘌呤。还已知此化合物的化学摘要名称是 L- 丙氨酸,N-[(S)-[[(1R)-2-(6- 胺基 -9H- 嘌呤 -9- 基)-1- 甲基乙氧基] 甲基] 苯氧基氧膦基]-,1- 甲基乙基酯。美国专利第 7,390,791 号和第 7,803,788 号公开了这种化合物的单反丁烯二酸形式和其制备方法 (参见例如实例 4)。

发明内容

[0012] 已确定当 GS-7340 与可比西他 (cobicistat,(2R,5R)-(5-{[(2S)-2-[(甲基 {[2-(丙 -2- 基)-1,3- 噻唑 -4- 基] 甲基 } 氨甲酰基) 氨基]]-4-(吗啉 -4- 基) 丁酰胺基 }-1,6- 二苯基己 -2- 基) 氨基甲酸 1,3- 噻唑 -5- 基甲酯) 一起投与时在人类中 GS-7340 的全身暴露改善。当与可比西他一起投与时,GS-7340 被计算为具有比单独 GS-7340 剂量高 2.2 倍的全身暴露当量。在另一情况下,与可比西他一起投与的 GS-7340 被计算为具有比单独 GS-7340 剂量高 3-4 倍的全身暴露当量。在另一情况下,与可比西他一起投与的 GS-7340 被计算为具有比单独 GS-7340 剂量高 1.3 倍的全身暴露当量。

[0013] 在一个实施例中,本发明提供化合物 GS-7340 或其医药学上可接受的盐和可比西他或其医药学上可接受的盐用于防治性或治疗性治疗人的病毒感染的用途。可比西他可与 GS-7340 共投与。GS-7340 或其医药学上可接受的盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。GS-7340 或其医药学上可接受的盐和可比西他或其医药学上可接受的盐可共投与。可使用包含每日量的 GS-7340 或其医药学上可接受的盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。病毒感染的病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0014] 在一个实施例中,本发明提供化合物 GS-7340 或其医药学上可接受的盐和可比西他或其医药学上可接受的盐用于改进 GS-7340 的药物动力学的用途。可比西他可与 GS-7340 共投与。GS-7340 或其医药学上可接受的盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。GS-7340 或其医药学上可接受的盐和

可比西他或其医药学上可接受的盐可共投与。可使用包含每日量的GS-7340或其医药学上可接受的盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0015] 在一个实施例中,本发明提供化合物GS-7340或其医药学上可接受的盐和可比西他或其医药学上可接受的盐用于改进GS-7340的C_{max}的用途。可比西他可与GS-7340共投与。GS-7340或其医药学上可接受的盐可以3mg、8±3mg、10±5mg、25±5mg或40±10mg或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以50-500mg、100-400mg、100-300mg或150mg的量使用。GS-7340或其医药学上可接受的盐和可比西他或其医药学上可接受的盐可共投与。可使用包含每日量的GS-7340或其医药学上可接受的盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0016] 在一个实施例中,本发明提供化合物GS-7340或其医药学上可接受的盐和可比西他或其医药学上可接受的盐用于改进GS-7340的血液水平的用途。可比西他可与GS-7340共投与。GS-7340或其医药学上可接受的盐可以3mg、8±3mg、10±5mg、25±5mg或40±10mg或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以50-500mg、100-400mg、100-300mg或150mg的量使用。GS-7340或其医药学上可接受的盐和可比西他或其医药学上可接受的盐可共投与。可使用包含每日量的GS-7340或其医药学上可接受的盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0017] 在一个实施例中,本发明提供一种组合物,其包含单位剂型的GS-7340或其医药学上可接受的盐;单位剂型的可比西他或其医药学上可接受的盐;和医药学上可接受的载剂或稀释剂。组合物可包括呈3mg、8±3mg、10±5mg、25±5mg或40±10mg或如下文阐述的其它范围的量的GS-7340或其医药学上可接受的盐。组合物可包括呈50-500mg、100-400mg、100-300mg或150mg的量的可比西他。单位剂型可为单次日剂量。

[0018] 在一个实施例中,本发明提供一种试剂盒,其包含:(1)GS-7340或其医药学上可接受的盐;(2)可比西他或其医药学上可接受的盐;(3)一或多个容器;和(4)关于投与GS-7340或其医药学上可接受的盐以及可比西他或其医药学上可接受的盐的处方信息。试剂盒可包括呈3mg、8±3mg、10±5mg、25±5mg或40±10mg或如下文阐述的其它范围的量的GS-7340或其医药学上可接受的盐。试剂盒可包括呈50-500mg、100-400mg、100-300mg或150mg的量的可比西他。

[0019] 在一个实施例中,本发明提供一种治疗人的病毒感染的方法,其包含共投与GS-7340以及可比西他或其医药学上可接受的盐,其中与GS-7340共投与的可比西他的剂量提供与在不存在可比西他的情况下通过投与较大剂量GS-7340可获得的全身暴露相当的GS-7340全身暴露。呈3mg、8±3mg、10±5mg、25±5mg或40±10mg或如下文阐述的其它范围的量的GS-7340或其医药学上可接受的盐可与可比西他共投与。呈50-500mg、100-400mg、100-300mg或150mg的量的可比西他可与GS-7340共投与。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0020] 在一个实施例中,本发明提供一种抑制人的逆转录病毒逆转录酶的活性的方法,其包含共投与GS-7340以及可比西他或其医药学上可接受的盐,其中与GS-7340共投与的

可比西他的剂量提供与在不存在可比西他的情况下通过投与较大剂量 GS-7340 可获得的全身暴露相当的 GS-7340 全身暴露。呈 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量的 GS-7340 或其医药学上可接受的盐可与可比西他共投与。呈 50-500mg、100-400mg、100-300mg 或 150mg 的量的可比西他可与 GS-7340 共投与。病毒可为人类免疫缺陷病毒 (HIV)。

[0021] 在一个实施例中，本发明提供与可比西他或其医药学上可接受的盐共投与的化合物 GS-7340 或其医药学上可接受的盐用于制造供治疗病毒感染用的药物的用途。本发明进一步提供与可比西他或其医药学上可接受的盐共投与的化合物 GS-7340 或其医药学上可接受的盐用于制造供治疗人的病毒感染用的药物的用途。GS-7340 或其医药学上可接受的盐可以次治疗量（或在整个一些实施例中以治疗量）使用。GS-7340 或其医药学上可接受的盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量 GS-7340 可获得的全身暴露相当的 GS-7340 全身暴露，用于制造药物。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0022] 在一个实施例中，本发明提供与可比西他或其医药学上可接受的盐共投与的化合物 GS-7340 或其医药学上可接受的盐用于制造供抑制逆转录病毒逆转录酶活性用的药物的用途。本发明进一步提供与可比西他或其医药学上可接受的盐共投与的化合物 GS-7340 或其医药学上可接受的盐用于制造供抑制人的逆转录病毒逆转录酶活性用的药物的用途。GS-7340 或其医药学上可接受的盐可以次治疗量使用。GS-7340 或其医药学上可接受的盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量 GS-7340 可获得的全身暴露相当的 GS-7340 全身暴露，用于制造药物。病毒可为人类免疫缺陷病毒 (HIV)。

[0023] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途，其用于制备适用于在投与人之后改进 GS-7340 或其医药学上可接受的盐的药物动力学的药物。GS-7340 或其医药学上可接受的盐可以次治疗量使用。GS-7340 或其医药学上可接受的盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如以下阐述的其它范围的量使用。可比西他可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量 GS-7340 可获得的全身暴露相当的 GS-7340 全身暴露，用于制造药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0024] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途，其用于制备适用于在投与人之后改进 {9-[(R)-2-[[(S)-[[(S)-1-（异丙氧基羰基）乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤} 或其医药学上可接受的盐的药物动力学的药物。GS-7340 或其医药学上可接受的盐可以次治疗量使用。{9-[(R)-2-[[(S)-[[(S)-1-（异丙氧基羰基）乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤} 或其医药学上可接受的盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如本文中阐述的其它范围的量使用。可比西他可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可比西他可以一定的

量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量 GS-7340 可获得的全身暴露相当的 GS-7340 全身暴露，用于制造药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0025] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途；其用于制备适用于在投与可比西他后使 GS-7340 或其医药学上可接受的盐的剂量减小约 30-70％的供人用的药物。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0026] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途；其用于制备适用于在投与可比西他后使GS-7340 或其医药学上可接受的盐的剂量减小约 2-4 倍的供人用的药物。在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途；其用于制备适用于在投与可比西他后使GS-7340 或其医药学上可接受的盐的剂量减小约 3 倍的供人用的药物。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0027] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 1)GS-7340 或其医药学上可接受的盐；和 2) 可比西他或其医药学上可接受的盐。GS-7340 或其医药学上可接受的盐以次治疗量投与。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0028] 在一个实施例中，本发明提供与可比西他共投与的次治疗剂量的 GS-7340 用于治疗病毒感染的用途。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0029] 在一个实施例中，本发明提供与可比西他共投与的次治疗剂量的 GS-7340 用于抑制逆转录病毒逆转录酶的用途。病毒可为人类免疫缺陷病毒 (HIV)。

[0030] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a) 化合物 GS-7340 或其医药学上可接受的盐和 (b) 可比西他或其医药学上可接受的盐。抗病毒剂可包括 GS-7340 或其医药学上可接受的盐，其可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。抗病毒剂可包括呈 50-500mg、100-400mg、100-300mg 或 150mg 的量的可比西他。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量 GS-7340 可获得的全身暴露相当的 GS-7340 全身暴露，用于制造药物。抗病毒剂可进一步包括 200mg 恩曲他滨 (emtricitabine) 和 150mg 埃替格韦 (elvitegravir)。抗病毒剂可进一步包括 150mg 可比西他、8mg 或 8mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可进一步包括 150mg 可比西他、25mg 或 25mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可进一步包括 150mg 可比西他、10mg 或 10mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可包括 150mg 可比西他、8mg GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可包括 150mg 可比西他、10mg GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。

[0031] 在一个实施例中，本发明提供单位剂量的 GS-7340 或其医药学上可接受的盐和可比西他或其医药学上可接受的盐，其中所述单位剂量是日剂量。GS-7340 可以次治疗量存在。单位剂量可进一步包括 150mg 可比西他、8mg 或 8mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。单位剂量可进一步包括 150mg 可比西他、25mg 或 25mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。单位剂量可进一步包括 150mg 可比西他、10mg 或 10mg

以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。单位剂量可包括 150mg 可比西他、10mg GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。

[0032] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途，其用于制备适用于在投与人之后改进 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐的药物动力学的药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可例如为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0033] 在一个实施例中，本发明提供可比西他，其用于在投与人之后改进 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐的药物动力学。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0034] 在一个实施例中，本发明提供一种试剂盒，其包含：(1) {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐；(2) 可比西他或其医药学上可接受的盐；(3) 一或多个容器；和 (4) 关于投与 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐以及可比西他或其医药学上可接受的盐的处方信息。

[0035] 在一个实施例中，本发明提供一种试剂盒，其包含：(1) 包含 5-100mg 的 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐的单位剂型；(2) 包含 150mg 可比西他或其医药学上可接受的盐的单位剂型；(3) 一或多个容器；和 (4) 关于投与 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐以及可比西他或其医药学上可接受的盐的处方信息。

[0036] 在一个实施例中，本发明提供 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐的用途，其用于制造供抑制人的逆转录病毒逆转录酶活性用的药物，包含向人投与 GS-7340 或其医药学上可接受的盐和可比西他或其医药学上可接受的盐。病毒可为人类免疫缺陷病毒 (HIV)。

[0037] 在一个实施例中，本发明提供 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐；和可比西他或其医药学上可接受的盐；用于抑制人的逆转录病毒逆转录酶活性。

[0038] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途，其用于制备适用于在投与可比西他后使 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐的剂量减小约 30-70％的供人用的药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0039] 在一个实施例中，本发明提供 {9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐和可比西他或其医药学上可接受的盐的用途，其用于防治性或治疗性治疗人的病毒感染。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒

(HBV)。

[0040] 在一个实施例中，本发明提供一种抗病毒剂，其包含(a){9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤}或其医药学上可接受的盐，其与(b)可比西他或其医药学上可接受的盐组合使用以用于防治性或治疗性治疗人的病毒感染。

[0041] 还已确定了人类中替诺福韦的全身暴露在替诺福韦与可比西他一起投与时改进。当与可比西他一起投与时，替诺福韦被计算为具有比单独替诺福韦剂量高3到4倍的全身暴露当量。

[0042] 在一个实施例中，本发明提供化合物替诺福韦或其医药学上可接受的盐和可比西他或其医药学上可接受的盐用于防治性或治疗性治疗人的病毒感染的用途。替诺福韦可以少于300mg、200mg或200mg以下和100mg或100mg以下的量使用。可比西他可以50-500mg、100-400mg、100-300mg和150mg的量使用。替诺福韦或其医药学上可接受的盐和可比西他或其医药学上可接受的盐可共投与。所述用途可提供投与包含每日量替诺福韦或其医药学上可接受的盐和每日量可比西他或其医药学上可接受的盐的单位剂型。病毒可为人类免疫缺陷病毒(HIV)。

[0043] 在一个实施例中，本发明提供一种组合物，其包含单位剂型的替诺福韦或其医药学上可接受的盐；单位剂型的可比西他或其医药学上可接受的盐；和医药学上可接受的载剂或稀释剂。替诺福韦可以少于300mg、200mg或200mg以下和100mg或100mg以下的量存在于组合物中。可比西他可以50-500mg、100-400mg、100-300mg和150mg的量使用。

[0044] 在一个实施例中，本发明提供一种试剂盒，其包括(1)替诺福韦或其医药学上可接受的盐；(2)可比西他或其医药学上可接受的盐；(3)一或多个容器；和(4)关于投与替诺福韦或其医药学上可接受的盐以及可比西他或其医药学上可接受的盐的处方信息。替诺福韦可以少于300mg、200mg或200mg以下和100mg或100mg以下的量存在于试剂盒中。可比西他可以50-500mg、100-400mg、100-300mg和150mg的量使用。

[0045] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包括共投与替诺福韦以及可比西他或其医药学上可接受的盐，其中与替诺福韦共投与的可比西他的剂量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦可获得的全身暴露相当的替诺福韦全身暴露。替诺福韦可以少于300mg、200mg或200mg以下和100mg或100mg以下的量投与。可比西他可以50-500mg、100-400mg、100-300mg和150mg的量投与。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0046] 在一个实施例中，本发明提供一种抑制人的逆转录病毒逆转录酶的活性的方法，其包含共投与替诺福韦以及可比西他或其医药学上可接受的盐，其中与可比西他共投与的替诺福韦的剂量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦可获得的全身暴露相当的替诺福韦全身暴露。替诺福韦可以少于300mg、200mg或200mg以下和100mg或100mg以下的量共投与。可比西他可以50-500mg、100-400mg、100-300mg和150mg的量共投与。病毒可为人类免疫缺陷病毒(HIV)。

[0047] 在一个实施例中，本发明提供与可比西他或其医药学上可接受的盐共投与的化合物替诺福韦或其医药学上可接受的盐用于制造供治疗病毒感染用的药物的用途。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒

(HBV)。

[0048] 在一个实施例中,本发明提供与可比西他或其医药学上可接受的盐共投与的化合物替诺福韦或其医药学上可接受的盐用于制造供治疗人的病毒感染用的药物的用途。替诺福韦或其医药学上可接受的盐可以次治疗量(或在整个一些实施例中以治疗量)使用。替诺福韦可以少于 300mg、200mg 或 200mg 以下和 100mg 或 100mg 以下的量投与。可比西他可以一定的量投与,所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦可获得的全身暴露相当的替诺福韦全身暴露,用于制造药物。呈 150mg 的量的可比西他可用于制造药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0049] 在一个实施例中,本发明提供与可比西他或其医药学上可接受的盐共投与的化合物替诺福韦或其医药学上可接受的盐用于制造供抑制逆转录病毒逆转录酶活性用的药物的用途。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0050] 在一个实施例中,本发明提供与可比西他或其医药学上可接受的盐共投与的化合物替诺福韦或其医药学上可接受的盐用于制造供抑制人的逆转录病毒逆转录酶活性用的药物的用途。替诺福韦或其医药学上可接受的盐可以次治疗量使用。替诺福韦可以少于 300mg、200mg 或 200mg 以下和 100mg 或 100mg 以下的量使用。可比西他可以一定的量共投与,所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦可获得的全身暴露相当的替诺福韦全身暴露,用于制造药物。可共投与呈 150mg 的量的可比西他。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0051] 在一个实施例中,本发明提供可比西他或其医药学上可接受的盐的用途,其用于制备适用于在投与人之后改进替诺福韦或其医药学上可接受的盐的药物动力学的药物。替诺福韦或其医药学上可接受的盐可以次治疗量使用。替诺福韦或其医药学上可接受的盐可以 100mg 或 100mg 以下、200mg 或 200mg 以下的量或以少于 300mg 的量共投与人。可比西他可以一定的量使用,所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦可获得的全身暴露相当的替诺福韦全身暴露,用于制造药物。呈 150mg 的量的可比西他可用于制备药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0052] 在一个实施例中,本发明提供可比西他或其医药学上可接受的盐的用途;其用于制备适用于在投与可比西他后使替诺福韦或其医药学上可接受的盐的剂量减小约 30-70%的供人用的药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0053] 在一个实施例中,本发明提供可比西他或其医药学上可接受的盐的用途;其用于制备适用于在投与可比西他后使替诺福韦或其医药学上可接受的盐的剂量减小约 2 到 4 倍的供人用的药物。在一个实施例中,本发明提供可比西他或其医药学上可接受的盐的用途;其用于制备适用于在投与可比西他后使替诺福韦或其医药学上可接受的盐的剂量减小约 3 倍的供人用的药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒(HIV)或乙型肝炎病毒(HBV)。

[0054] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与1）替诺福韦或其医药学上可接受的盐；和2）可比西他或其医药学上可接受的盐。替诺福韦或其医药学上可接受的盐可以次治疗量投与。病毒可为人类免疫缺陷病毒（HIV）或乙型肝炎病毒（HBV）。

[0055] 在一个实施例中，本发明提供与可比西他共投与的次治疗剂量的替诺福韦用于治疗病毒感染的用途。病毒可为人类免疫缺陷病毒（HIV）或乙型肝炎病毒（HBV）。

[0056] 在一个实施例中，本发明提供与可比西他共投与的次治疗剂量的替诺福韦用于抑制逆转录病毒逆转录酶的用途。病毒可为人类免疫缺陷病毒（HIV）。

[0057] 在一个实施例中，本发明提供一种抗病毒剂，其包含（a）化合物替诺福韦或其医药学上可接受的盐和（b）可比西他或其医药学上可接受的盐。替诺福韦可以次治疗量存在于抗病毒剂中。替诺福韦可以100mg或100mg以下、200mg或200mg以下或少于300mg的量存在于抗病毒剂中。与替诺福韦共投与的可比西他可以一定的量存在于抗病毒剂中，所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦可获得的全身暴露相当的替诺福韦全身暴露。抗病毒剂可进一步包括呈150mg的量的可比西他。抗病毒剂可进一步包括200mg恩曲他滨和150mg埃替格韦。抗病毒剂可包括150mg可比西他、100mg或100mg以下替诺福韦、150mg埃替格韦和200mg恩曲他滨。抗病毒剂可包括150mg可比西他、200mg或200mg以下替诺福韦、150mg埃替格韦和200mg恩曲他滨。抗病毒剂可包括150mg可比西他、少于300mg替诺福韦、150mg埃替格韦和200mg恩曲他滨。抗病毒剂可包括150mg可比西他、50mg替诺福韦、150mg埃替格韦和200mg恩曲他滨。病毒可为人类免疫缺陷病毒（HIV）或乙型肝炎病毒（HBV）。

[0058] 在一个实施例中，本发明提供单位剂量的替诺福韦或其医药学上可接受的盐和可比西他或其医药学上可接受的盐，其中所述单位剂量是日剂量。替诺福韦可以次治疗量存在。单位剂量可包括100mg或100mg以下、200mg或200mg以下或少于300mg替诺福韦。单位剂量可包括一定的量的可比西他，所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦可获得的全身暴露相当的替诺福韦全身暴露。单位剂量可包括150mg可比西他。病毒可为人类免疫缺陷病毒（HIV）或乙型肝炎病毒（HBV）。

[0059] 还描述了9-[(R)-2-[[(S)-[[(S)-1-（异丙氧基羰基）乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤的半反丁烯二酸盐形式。9-[(R)-2-[[(S)-[[(S)-1-（异丙氧基羰基）乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤（GS-7340）的名称是替诺福韦艾拉酚胺（tenofovir alafenamide）。替诺福韦艾拉酚胺的半反丁烯二酸盐形式在本文中也被称为替诺福韦艾拉酚胺半反丁烯二酸盐。

[0060] 在本发明的一个实施例中提供替诺福韦艾拉酚胺半反丁烯二酸盐，尤其与可比西他和/或其它另外的治疗剂组合。

[0061] 在另一实施例中提供其中反丁烯二酸与替诺福韦艾拉酚胺之比是0.5±0.1或0.5±0.05或0.5±0.01或约0.5的替诺福韦艾拉酚胺半反丁烯二酸盐。

[0062] 在一个实施例中提供呈固体形式的替诺福韦艾拉酚胺半反丁烯二酸盐。

[0063] 在一个实施例中提供X射线粉末衍射（XRPD）图案的2θ值是6.9±0.2°和8.6±0.2°的替诺福韦艾拉酚胺半反丁烯二酸盐。在另一实施例中提供其中XRPD图案的2θ值包含6.9±0.2°、8.6±0.2°、11.0±0.2°、15.9±0.2°和20.2±0.2°的替诺福

韦艾拉酚胺半反丁烯二酸盐。

[0064] 在一个实施例中提供差示扫描量热法(DSC)的起始吸热线是131±2℃或131±1℃的替诺福韦艾拉酚胺半反丁烯二酸盐。

[0065] 在一个实施例中提供一种医药组合物,其包含替诺福韦艾拉酚胺半反丁烯二酸盐和医药学上可接受的赋形剂。在另一实施例中提供所述医药组合物,其进一步包含另外的治疗剂。在另一实施例中,另外的治疗剂选自由以下组成的群组:人类免疫缺陷病毒(HIV)蛋白酶抑制化合物、HIV逆转录酶的非核苷抑制剂、HIV逆转录酶的核苷抑制剂、HIV逆转录酶的核苷酸抑制剂、HIV整合酶抑制剂、CCR5抑制剂和另外的蛋白酶抑制化合物。

[0066] 在一个实施例中提供一种用于治疗人类免疫缺陷病毒(HIV)感染的方法,其包含向有需要的个体投与治疗有效量的替诺福韦艾拉酚胺半反丁烯二酸盐。在另一实施例中提供一种用于治疗HIV感染的方法,其包含向有需要的个体投与治疗有效量的包含替诺福韦艾拉酚胺半反丁烯二酸盐的医药组合物。在另一实施例中,所述方法包含向个体投与一或多种选自由以下组成的群组的另外的治疗剂:HIV蛋白酶抑制化合物、HIV逆转录酶的非核苷抑制剂、HIV逆转录酶的核苷抑制剂、HIV逆转录酶的核苷酸抑制剂、HIV整合酶抑制剂、CCR5抑制剂和另外的蛋白酶抑制化合物。

[0067] 在一个实施例中提供一种用于治疗乙型肝炎病毒(HBV)感染的方法,其包含向有需要的个体投与治疗有效量的替诺福韦艾拉酚胺半反丁烯二酸盐。在另一实施例中提供一种用于治疗HBV感染的方法,其包含向有需要的个体投与治疗有效量的包含替诺福韦艾拉酚胺半反丁烯二酸盐的医药组合物。

[0068] 在一个实施例中提供一种用于制备医药组合物的方法,其包含将替诺福韦艾拉酚胺半反丁烯二酸盐与医药学上可接受的赋形剂组合来提供所述医药组合物。

[0069] 在一个实施例中提供用于医学疗法的替诺福韦艾拉酚胺半反丁烯二酸盐。

[0070] 在一个实施例中提供替诺福韦艾拉酚胺半反丁烯二酸盐用于防治性或治疗性治疗HIV感染的用途。在另一实施例中提供替诺福韦艾拉酚胺半反丁烯二酸盐治疗HIV感染的用途。在另一实施例中提供替诺福韦艾拉酚胺半反丁烯二酸盐用于制备或制造供治疗HIV感染用的药物的用途。在再另一实施例中提供用于治疗HIV感染的替诺福韦艾拉酚胺半反丁烯二酸盐。

[0071] 在一个实施例中提供替诺福韦艾拉酚胺半反丁烯二酸盐用于防治性或治疗性治疗HBV感染的用途。在另一实施例中提供替诺福韦艾拉酚胺半反丁烯二酸盐治疗HBV感染的用途。在另一实施例中提供替诺福韦艾拉酚胺半反丁烯二酸盐用于制备或制造供治疗HBV感染用的药物的用途。在再另一实施例中提供用于治疗HBV感染的替诺福韦艾拉酚胺半反丁烯二酸盐。

[0072] 在本发明的一些实施例中,治疗方法及其类似方法包含投与多个日剂量。在其它实施例中,治疗方法及其类似方法包含投与单次日剂量。

[0073] 在一个实施例中,本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐用于防治性或治疗性治疗人的病毒感染的用途。可比西他可与替诺福韦艾拉酚胺半反丁烯二酸盐共投与。替诺福韦艾拉酚胺半反丁烯二酸盐可以3mg、8±3mg、10±5mg、25±5mg或40±10mg或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以50-500mg、100-400mg、100-300mg或150mg的量使用。可共投与替诺福韦

艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐。可使用包含每日量的替诺福韦艾拉酚胺半反丁烯二酸盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0074] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐用于改进替诺福韦艾拉酚胺半反丁烯二酸盐的药物动力学的用途。可比西他可与替诺福韦艾拉酚胺半反丁烯二酸盐共投与。替诺福韦艾拉酚胺半反丁烯二酸盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可共投与替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐。可使用包含每日量的替诺福韦艾拉酚胺半反丁烯二酸盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0075] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐用于改进替诺福韦艾拉酚胺半反丁烯二酸盐的 C_{max} 的用途。可比西他可与替诺福韦艾拉酚胺半反丁烯二酸盐共投与。替诺福韦艾拉酚胺半反丁烯二酸盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可共投与替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐。可使用包含每日量的替诺福韦艾拉酚胺半反丁烯二酸盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0076] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐用于改进替诺福韦艾拉酚胺半反丁烯二酸盐的血液水平的用途。可比西他可与替诺福韦艾拉酚胺半反丁烯二酸盐共投与。替诺福韦艾拉酚胺半反丁烯二酸盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他或其医药学上可接受的盐可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可共投与替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐。可使用包含每日量的替诺福韦艾拉酚胺半反丁烯二酸盐和每日量的可比西他或其医药学上可接受的盐的单位剂型。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0077] 在一个实施例中，本发明提供一种组合物，其包含单位剂型的替诺福韦艾拉酚胺半反丁烯二酸盐；单位剂型的可比西他或其医药学上可接受的盐；和医药学上可接受的载剂或稀释剂。组合物可包括呈 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量的替诺福韦艾拉酚胺半反丁烯二酸盐。组合物可包括呈 50-500mg、100-400mg、100-300mg 或 150mg 的量的可比西他。单位剂型可为单次日剂量。

[0078] 在一个实施例中，本发明提供一种试剂盒，其包含：(1) 替诺福韦艾拉酚胺半反丁烯二酸盐；(2) 可比西他或其医药学上可接受的盐；(3) 一或多个容器；和 (4) 关于投与替诺福韦艾拉酚胺半反丁烯二酸盐以及可比西他或其医药学上可接受的盐的处方信息。试剂盒可包括呈 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量的

替诺福韦艾拉酚胺半反丁烯二酸盐。试剂盒可包括呈 50-500mg、100-400mg、100-300mg 或 150mg 的量的可比西他。

[0079] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含共投与替诺福韦艾拉酚胺半反丁烯二酸盐以及可比西他或其医药学上可接受的盐，其中与替诺福韦艾拉酚胺半反丁烯二酸盐共投与的可比西他的剂量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦艾拉酚胺半反丁烯二酸盐可获得的全身暴露相当的替诺福韦艾拉酚胺半反丁烯二酸盐全身暴露。呈 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量的替诺福韦艾拉酚胺半反丁烯二酸盐可与可比西他共投与。呈 50-500mg、100-400mg、100-300mg 或 150mg 的量的可比西他可与替诺福韦艾拉酚胺半反丁烯二酸盐共投与。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0080] 在一个实施例中，本发明提供一种用于抑制人的逆转录病毒逆转录酶的活性的方法，其包含共投与替诺福韦艾拉酚胺半反丁烯二酸盐以及可比西他或其医药学上可接受的盐，其中与替诺福韦艾拉酚胺半反丁烯二酸盐共投与的可比西他的剂量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦艾拉酚胺半反丁烯二酸盐可获得的全身暴露相当的替诺福韦艾拉酚胺半反丁烯二酸盐全身暴露。呈 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量的替诺福韦艾拉酚胺半反丁烯二酸盐或其医药学上可接受的盐可与可比西他共投与。呈 50-500mg、100-400mg、100-300mg 或 150mg 的量的可比西他可与替诺福韦艾拉酚胺半反丁烯二酸盐共投与。病毒可为人类免疫缺陷病毒 (HIV)。

[0081] 在一个实施例中，本发明提供与可比西他或其医药学上可接受的盐共投与的替诺福韦艾拉酚胺半反丁烯二酸盐用于制造供治疗病毒感染用的药物的用途。本发明进一步提供与可比西他或其医药学上可接受的盐共投与的替诺福韦艾拉酚胺半反丁烯二酸盐用于制造供治疗人的病毒感染用的药物的用途。替诺福韦艾拉酚胺半反丁烯二酸盐可以次治疗量（或在整个一些实施例中，以治疗量）使用。替诺福韦艾拉酚胺半反丁烯二酸盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦艾拉酚胺半反丁烯二酸盐可获得的全身暴露相当的替诺福韦艾拉酚胺半反丁烯二酸盐全身暴露，用于制造药物。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0082] 在一个实施例中，本发明提供与可比西他或其医药学上可接受的盐共投与的替诺福韦艾拉酚胺半反丁烯二酸盐用于制造供抑制逆转录病毒逆转录酶活性用的药物的用途。本发明进一步提供与可比西他或其医药学上可接受的盐共投与的替诺福韦艾拉酚胺半反丁烯二酸盐用于制造供抑制人的逆转录病毒逆转录酶活性用的药物的用途。替诺福韦艾拉酚胺半反丁烯二酸盐可以次治疗量使用。替诺福韦艾拉酚胺半反丁烯二酸盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦艾拉酚胺半反丁烯二酸盐可获得的全身暴露相当的替诺福韦艾拉酚胺半反丁烯二酸盐全身暴露，用于制造药物。病毒可为人类免疫缺陷病毒 (HIV)。

[0083] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途，其用于

制备适用于在投与人之后改进替诺福韦艾拉酚胺半反丁烯二酸盐的药物动力学的药物。替诺福韦艾拉酚胺半反丁烯二酸盐可以次治疗量使用。替诺福韦艾拉酚胺半反丁烯二酸盐可以 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量使用。可比西他可以 50-500mg、100-400mg、100-300mg 或 150mg 的量使用。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦艾拉酚胺半反丁烯二酸盐可获得的全身暴露相当的替诺福韦艾拉酚胺半反丁烯二酸盐全身暴露，用于制造药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0084] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途；其用于制备适用于在投与可比西他后使替诺福韦艾拉酚胺半反丁烯二酸盐的剂量减小约 30-70％的供人用的药物。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0085] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途；其用于制备适用于在投与可比西他后使替诺福韦艾拉酚胺半反丁烯二酸盐的剂量减小约 2-4 倍的供人用的药物。在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途；其用于制备适用于在投与可比西他后使替诺福韦艾拉酚胺半反丁烯二酸盐的剂量减小约 3 倍的供人用的药物。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0086] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 1) 替诺福韦艾拉酚胺半反丁烯二酸盐；和 2) 可比西他或其医药学上可接受的盐。替诺福韦艾拉酚胺半反丁烯二酸盐以次治疗量投与。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0087] 在一个实施例中，本发明提供与可比西他共投与的次治疗剂量的替诺福韦艾拉酚胺半反丁烯二酸盐用于治疗病毒感染的用途。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0088] 在一个实施例中，本发明提供与可比西他共投与的次治疗剂量的替诺福韦艾拉酚胺半反丁烯二酸盐用于抑制逆转录病毒逆转录酶的用途。病毒可为人类免疫缺陷病毒 (HIV)。

[0089] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐和 (b) 可比西他或其医药学上可接受的盐。抗病毒剂可包括呈 3mg、8±3mg、10±5mg、25±5mg 或 40±10mg 或如下文阐述的其它范围的量的替诺福韦艾拉酚胺半反丁烯二酸盐。抗病毒剂可包括呈 50-500mg、100-400mg、100-300mg 或 150mg 的量的可比西他。可比西他可以一定的量使用，所述量提供与在不存在可比西他的情况下通过投与较大剂量替诺福韦艾拉酚胺半反丁烯二酸盐可获得的全身暴露相当的替诺福韦艾拉酚胺半反丁烯二酸盐全身暴露，用于制造药物。抗病毒剂可进一步包括 200mg 恩曲他滨和 150mg 埃替格韦。抗病毒剂可进一步包括 150mg 可比西他、8mg 或 8mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可进一步包括 150mg 可比西他、25mg 或 25mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可进一步包括 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、

150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可包括 150mg 可比西他、8mg 替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。抗病毒剂可包括 150mg 可比西他、10mg 替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。

[0090] 在一个实施例中，本发明提供单位剂量的替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐，其中所述单位剂量是日剂量。替诺福韦艾拉酚胺半反丁烯二酸盐可以次治疗量存在。单位剂量可进一步包括 150mg 可比西他、8mg 或 8mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。单位剂量可进一步包括 150mg 可比西他、25mg 或 25mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。单位剂量可进一步包括 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。单位剂量可包括 150mg 可比西他、10mg 替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。

[0091] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途，其用于制备适用于在投与人之后改进替诺福韦艾拉酚胺半反丁烯二酸盐的药物动力学的药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0092] 在一个实施例中，本发明提供用于在投与人之后改进替诺福韦艾拉酚胺半反丁烯二酸盐的药物动力学的可比西他。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0093] 在一个实施例中，本发明提供一种试剂盒，其包含 :(1) 替诺福韦艾拉酚胺半反丁烯二酸盐 ;(2) 可比西他或其医药学上可接受的盐 ;(3) 一或多个容器 ;和 (4) 关于投与替诺福韦艾拉酚胺半反丁烯二酸盐以及可比西他或其医药学上可接受的盐的处方信息。

[0094] 在一个实施例中，本发明提供一种试剂盒，其包含 :(1) 包含 5-100mg 替诺福韦艾拉酚胺半反丁烯二酸盐的单位剂型 ;(2) 包含 150mg 可比西他或其医药学上可接受的盐的单位剂型 ;(3) 一或多个容器 ;和 (4) 关于投与替诺福韦艾拉酚胺半反丁烯二酸盐以及可比西他或其医药学上可接受的盐的处方信息。

[0095] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐的用途，其用于制造供抑制人的逆转录病毒逆转录酶活性用的药物，包含向人投与替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐。病毒可为人类免疫缺陷病毒 (HIV)。

[0096] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐，其用于抑制人的逆转录病毒逆转录酶活性。

[0097] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐的用途，其用于制备适用于在投与可比西他后使替诺福韦艾拉酚胺半反丁烯二酸盐的剂量减小约 30-70％的供人用的药物。药物可用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0098] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和可比西他或其医药学上可接受的盐用于防治性或治疗性治疗人的病毒感染的用途。用途可为用于防治性或治疗性治疗人的病毒感染。病毒可为人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0099] 在一个实施例中，本发明提供一种抗病毒剂，其包含 :(a) 替诺福韦艾拉酚胺半反丁烯二酸盐，其与 (b) 可比西他或其医药学上可接受的盐组合使用，用于防治性或治疗性

治疗人的病毒感染。

[0100] 在一个实施例中，本发明提供利托那韦 (ritonavir) 在以上阐述的组合物、试剂盒、单位剂量和用途中代替可比西他的用途。

[0101] 在一个实施例中，本发明提供一种用于在人中抑制 GS-7340 或其医药学上可接受的盐的 Pgp 介导的肠道分泌的方法，其通过共投与可比西他或其医药学上可接受的盐以及 GS-7340 或其医药学上可接受的盐进行。在一个实施例中，150mg 可比西他或其医药学上可接受的盐与 10mg GS-7340 或其医药学上可接受的盐共投与。

[0102] 在一个实施例中，本发明提供一种用于在人中抑制替诺福韦艾拉酚胺半反丁烯二酸盐的 Pgp 介导的肠道分泌的方法，其通过共投与可比西他或其医药学上可接受的盐以及替诺福韦艾拉酚胺半反丁烯二酸盐进行。在一个实施例中，150mg 可比西他或其医药学上可接受的盐与 10mg 替诺福韦艾拉酚胺半反丁烯二酸盐共投与。

[0103] 在一个实施例中，本发明提供抗病毒剂的用途，其用于防治性或治疗性治疗人的病毒感染，其中所述抗病毒剂包含 150mg 可比西他、10mg 或 10mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。

[0104] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 150mg 可比西他、10mg 或 10mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨。

[0105] 在一个实施例中，本发明提供 150mg 可比西他、10mg 或 10mg 以下 GS-7340、150mg 埃替格韦和 200mg 恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。

[0106] 在一个实施例中，本发明提供抗病毒剂的用途，其用于防治性或治疗性治疗人的病毒感染，其中所述抗病毒剂包含 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。

[0107] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨。

[0108] 在一个实施例中，本发明提供 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、150mg 埃替格韦和 200mg 恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。

[0109] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐、(b) 可比西他或其医药学上可接受的盐、(c) 恩曲他滨和 (d) 地瑞那韦 (darunavir)。

[0110] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a)8mg 或 8mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、(b)150mg 可比西他或其医药学上可接受的盐、(c)200mg 恩曲他滨和 (d)800mg 地瑞那韦。

[0111] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a)25mg 或 25mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、(b)150mg 可比西他或其医药学上可接受的盐、(c)200mg 恩曲他滨和 (d)800mg 地瑞那韦。

[0112] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a)10mg 替诺福韦艾拉酚胺半反丁烯二酸盐、(b)150mg 可比西他或其医药学上可接受的盐、(c)200mg 恩曲他滨和 (d)800mg 地瑞那韦。

[0113] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a)GS-7340 或其医药学上可接受的盐、(b) 可比西他或其医药学上可接受的盐、(c) 恩曲他滨和 (d) 地瑞那韦。

[0114] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a)8mg 或 8mg 以下 GS-7340 或其医药学上可接受的盐、(b)150mg 可比西他或其医药学上可接受的盐、(c)200mg 恩曲他滨和 (d)800mg 地瑞那韦。

[0115] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a)25mg 或 25mg 以下 GS-7340 或其医药学上可接受的盐、(b)150mg 可比西他或其医药学上可接受的盐、(c)200mg 恩曲他滨和 (d)800mg 地瑞那韦。

[0116] 在一个实施例中，本发明提供一种抗病毒剂，其包含 (a)10mg GS-7340 或其医药学上可接受的盐、(b)150mg 可比西他或其医药学上可接受的盐、(c)200mg 恩曲他滨和 (d)800mg 地瑞那韦。

[0117] 在一个实施例中，本发明提供抗病毒剂的用途，其用于防治性或治疗性治疗人的病毒感染，其中所述抗病毒剂包含 150mg 可比西他、10mg 或 10mg 以下 GS-7340、800mg 地瑞那韦和 200mg 恩曲他滨。

[0118] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 150mg 可比西他、10mg 或 10mg 以下 GS-7340、800mg 地瑞那韦和 200mg 恩曲他滨。

[0119] 在一个实施例中，本发明提供 150mg 可比西他、10mg 或 10mg 以下 GS-7340、800mg 地瑞那韦和 200mg 恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。

[0120] 在一个实施例中，本发明提供抗病毒剂的用途，其用于防治性或治疗性治疗人的病毒感染，其中所述抗病毒剂包含 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、800mg 地瑞那韦和 200mg 恩曲他滨。

[0121] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、800mg 地瑞那韦和 200mg 恩曲他滨。

[0122] 在一个实施例中，本发明提供 150mg 可比西他、10mg 或 10mg 以下替诺福韦艾拉酚胺半反丁烯二酸盐、800mg 地瑞那韦和 200mg 恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。

[0123] 在一个实施例中，本发明提供一定剂量的细胞色素 p450 抑制剂或其医药学上可接受的盐增强一定剂量的 GS-7340 或其医药学上可接受的盐的用途，其用于防治性或治疗性治疗人的病毒感染。在一个实施例中，细胞色素 p450 抑制剂是可比西他或其医药学上可接受的盐。在一个另外的实施例中，GS-7340 的剂量将为不存在可比西他剂量的次治疗量。

[0124] 在一个实施例中，本发明提供一种组合物，其包含 :单位剂型的 GS-7340 或其医药学上可接受的盐 ;单位剂型的可比西他或其医药学上可接受的盐 ;和医药学上可接受的载剂或稀释剂，其中单位剂型中 GS-7340 的量是次治疗量。

[0125] 在一个实施例中，本发明提供一定剂量的细胞色素 p450 抑制剂或其医药学上可接受的盐增强一定剂量的替诺福韦艾拉酚胺半反丁烯二酸盐的用途，其用于防治性或治疗性治疗人的病毒感染。在一个实施例中，细胞色素 p450 抑制剂是可比西他或其医药学上可接受的盐。在一个另外的实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐的剂量将为不存在可比西他剂量的次治疗量。

[0126] 在一个实施例中，本发明提供一种组合物，其包含：单位剂型的替诺福韦艾拉酚胺半反丁烯二酸盐；单位剂型的可比西他或其医药学上可接受的盐；和医药学上可接受的载剂或稀释剂，其中单位剂型中替诺福韦艾拉酚胺半反丁烯二酸盐的量是次治疗量。

[0127] 在一个实施例中，本发明提供关于如本文中所指出治疗病毒感染的用途和方法，其中所述病毒感染是人类免疫缺陷病毒 (HIV)。

[0128] 在一个实施例中，本发明提供关于如本文中所指出治疗病毒感染的用途和方法，其中所述病毒感染是乙型肝炎病毒 (HBV)。

[0129] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与包含可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的组合物，其中所述组合物包含一定量的可比西他或其医药学上可接受的盐，所述量足以使组合物中替诺福韦艾拉酚胺半反丁烯二酸盐的量提供对病毒感染的作用，所述作用比在不存在可比西他或其医药学上可接受的盐的情况下所述量的替诺福韦艾拉酚胺半反丁烯二酸盐的作用大，且其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0130] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与包含可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的组合物，其中组合物中替诺福韦艾拉酚胺半反丁烯二酸盐的量对病毒感染的作用比在不存在可比西他或其医药学上可接受的盐的情况下相同量的替诺福韦艾拉酚胺半反丁烯二酸盐的作用大，且其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0131] 在一个实施例中，本发明提供了一种关于人的病毒感染的抗病毒治疗方法，其包含向人投与包含可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半富马酸盐的组合物，其中所述组合物含有对于组合物中替诺福韦艾拉酚胺半富马酸盐的量充足的可比西他或其医药学上可接受的盐的量，从而提供比在不存在可比西他或其医药学上可接受的盐下所述量的替诺福韦艾拉酚胺半富马酸盐的抗病毒作用大的抗病毒作用，且其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0132] 在一个实施例中，本发明提供一种关于人的病毒感染的抗病毒治疗方法，其包含向人投与包含可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的组合物，其中组合物中替诺福韦艾拉酚胺半反丁烯二酸盐的量的抗病毒作用比在不存在可比西他或其医药学上可接受的盐的情况下相同量的替诺福韦艾拉酚胺半反丁烯二酸盐的抗病毒作用大，且其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0133] 在一个实施例中，本发明提供一种组合物，其包含：可比西他或其医药学上可接受的盐；和替诺福韦艾拉酚胺半反丁烯二酸盐。在另一实施例中，组合物包含：50-500mg 可比西他或其医药学上可接受的盐；和 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐。在另一实施例中，组合物进一步包含医药学上可接受的载剂或稀释剂。

[0134] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与一种组合物，所述组合物包含：可比西他或其医药学上可接受的盐；和替诺福韦艾拉酚胺半反丁烯二酸盐。

[0135] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐。

[0136] 在一个实施例中，本发明提供一种抑制逆转录病毒逆转录酶活性的方法，其包含

共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐。在另一实施例中，可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐的共投与是在人中。

[0137] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐用于防治性或治疗性治疗人的病毒感染的用途。

[0138] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐用于制造供治疗人的病毒感染用的药物的用途。

[0139] 在一个实施例中，本发明提供可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐用于制造供抑制逆转录病毒逆转录酶活性用的药物的用途。在另一实施例中，药物用于抑制人的逆转录病毒逆转录酶活性。

[0140] 在一个实施例中，本发明提供一种在人中增强替诺福韦艾拉酚胺半反丁烯二酸盐的抗病毒作用的方法，其包含向人投与一种组合物，所述组合物包含：可比西他或其医药学上可接受的盐；和替诺福韦艾拉酚胺半反丁烯二酸盐。

[0141] 在一个实施例中，本发明提供一种在人中增强替诺福韦艾拉酚胺半反丁烯二酸盐的抗病毒作用的方法，其包含向人共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐。在另一实施例中，50-500mg 可比西他或其医药学上可接受的盐与 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐共投与。

[0142] 在一个实施例中，本发明提供一种在人中抑制替诺福韦艾拉酚胺半反丁烯二酸盐的 Pgp 介导的肠道分泌的方法，其包含向人投与一种组合物，所述组合物包含：可比西他或其医药学上可接受的盐；和替诺福韦艾拉酚胺半反丁烯二酸盐。

[0143] 在一个实施例中，本发明提供一种用于在人中抑制替诺福韦艾拉酚胺半反丁烯二酸盐的 Pgp 介导的肠道分泌的方法，其通过共投与可比西他或其医药学上可接受的盐和替诺福韦艾拉酚胺半反丁烯二酸盐进行。在另一实施例中，50-500mg 可比西他或其医药学上可接受的盐与 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐共投与。

[0144] 在另外的实施例中，本发明提供所公开的方法和用途，其中病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0145] 在一个实施例中，本发明提供一种组合物，其包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦。在另一实施例中，组合物包含：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦。在另一实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与所述组合物。

[0146] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦。在另一实施例中，所述方法包含向人共投与 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦。

[0147] 在一个实施例中，本发明提供一种组合物的用途，所述组合物包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦，其用于防治性或治疗性治疗人的病毒感染。

[0148] 在一个实施例中，本发明提供 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦的用途，其用于制造供治疗人的病毒感染用的药物。在另一实施例中，本发明提供 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦的用途，其用于制造供治疗人的病毒感染用的药物。

[0149] 在一个实施例中，本发明提供一种组合物，其包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 埃替格韦，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0150] 在一个实施例中，本发明提供一种组合物，其包含：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)50-500mg 埃替格韦，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0151] 在另外的实施例中，本发明提供所公开的方法和用途，其中病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0152] 在一个实施例中，本发明提供一种组合物，其包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 地瑞那韦。在另一实施例中，组合物包含：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)400-1600mg 地瑞那韦。在另一实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与所述组合物。

[0153] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 地瑞那韦。在另一实施例中，所述方法包含向人共投与 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)400-1600mg 地瑞那韦。

[0154] 在一个实施例中，本发明提供一种组合物的用途，所述组合物包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 地瑞那韦，其用于防治性或治疗性治疗人的病毒感染。

[0155] 在一个实施例中，本发明提供 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 地瑞那韦的用途，其用于制造供治疗人的病毒感染用的药物。在另一实施例中，本发明提供 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)400-1600mg 地瑞那韦的用途，其用于制造供治疗人的病毒感染用的药物。

[0156] 在一个实施例中，本发明提供一种组合物，其包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 可比西他或其医药学上可接受的盐；(c) 恩曲他滨；和 (d) 地瑞那韦，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0157] 在一个实施例中，本发明提供一种组合物，其包含：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)50-500mg 可比西他或其医药学上可接受的盐；(c)50-500mg 恩曲他滨；和 (d)400-1600mg 地瑞那韦，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0158] 在另外的实施例中，本发明提供所公开的方法和用途，其中病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0159] 在一个实施例中，本发明提供一种组合物，其包含 ：替诺福韦艾拉酚胺半反丁烯二酸盐和恩曲他滨。在另一实施例中，组合物包含 ：3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 50-500mg 恩曲他滨。在另一实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与所述组合物。

[0160] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与替诺福韦艾拉酚胺半反丁烯二酸盐和恩曲他滨。在另一实施例中，所述方法包含向人共投与 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 50-500mg 恩曲他滨。

[0161] 在一个实施例中，本发明提供一种组合物的用途，所述组合物包含 ：替诺福韦艾拉酚胺半反丁烯二酸盐和恩曲他滨，其用于防治性或治疗性治疗人的病毒感染。

[0162] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。在另一实施例中，本发明提供 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 50-500mg 恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。

[0163] 在一个实施例中，本发明提供一种组合物，其包含 ：替诺福韦艾拉酚胺半反丁烯二酸盐和恩曲他滨，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0164] 在一个实施例中，本发明提供一种组合物，其包含 ：3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 50-500mg 恩曲他滨，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0165] 在另外的实施例中，本发明提供所公开的方法和用途，其中病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0166] 在一个实施例中，本发明提供一种组合物，其包含 ：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐 ；(b) 利匹韦林 (rilpivirine) ；和 (c) 恩曲他滨。在另一实施例中，组合物包含 ：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐 ；(b)10-80mg 利匹韦林 ；和 (c)50-500mg 恩曲他滨。在另一实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与所述组合物。

[0167] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐 ；(b) 利匹韦林 ；和 (c) 恩曲他滨。在另一实施例中，所述方法包含向人共投与 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐 ；(b)10-80mg 利匹韦林 ；和 (c)50-500mg 恩曲他滨。

[0168] 在一个实施例中，本发明提供一种组合物的用途，所述组合物包含 ：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐 ；(b) 利匹韦林 ；和 (c) 恩曲他滨，其用于防治性或治疗性治疗人的病毒感染。

[0169] 在一个实施例中，本发明提供 (a) 替诺福韦艾拉酚胺半反丁烯二酸盐 ；(b) 利匹韦林 ；和 (c) 恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。在另一实施例中本发明提供 (a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐 ；(b)10-80mg 利匹韦林 ；和 (c)50-500mg 恩曲他滨的用途，其用于制造供治疗人的病毒感染用的药物。

[0170] 在一个实施例中，本发明提供一种组合物，其包含：(a) 替诺福韦艾拉酚胺半反丁烯二酸盐；(b) 利匹韦林；和 (c) 恩曲他滨，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0171] 在一个实施例中，本发明提供一种组合物，所述组合物包含：(a)3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐；(b)10-80mg 利匹韦林；和 (c)50-500mg 恩曲他滨，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0172] 在另外的实施例中，本发明提供所公开的方法和用途，其中病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0173] 在一个实施例中，本发明提供一种组合物，其包含：替诺福韦艾拉酚胺半反丁烯二酸盐和 GS-9441。在另一实施例中，组合物包含：3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 5-1500mg GS-9441。在另一实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人投与所述组合物。

[0174] 在一个实施例中，本发明提供一种治疗人的病毒感染的方法，其包含向人共投与替诺福韦艾拉酚胺半反丁烯二酸盐和 GS-9441。在另一实施例中，所述方法包含向人共投与 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 5-1500mg GS-9441。

[0175] 在一个实施例中，本发明提供一种组合物的用途，所述组合物包含：替诺福韦艾拉酚胺半反丁烯二酸盐和 GS-9441，其用于防治性或治疗性治疗人的病毒感染。

[0176] 在一个实施例中，本发明提供替诺福韦艾拉酚胺半反丁烯二酸盐和 GS-9441 的用途，其用于制造供治疗人的病毒感染用的药物。在另一实施例中，本发明提供 3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 5-1500mg GS-9441 的用途，其用于制造供治疗人的病毒感染用的药物。

[0177] 在一个实施例中，本发明提供一种组合物，其包含：替诺福韦艾拉酚胺半反丁烯二酸盐和 GS-9441，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0178] 在一个实施例中，本发明提供一种组合物，其包含：3-40mg 替诺福韦艾拉酚胺半反丁烯二酸盐和 5-1500mg GS-9441，其用于治疗病毒感染，其中所述病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

[0179] 在另外的实施例中，本发明提供所公开的方法和用途，其中病毒感染是人类免疫缺陷病毒 (HIV) 或乙型肝炎病毒 (HBV)。

附图说明

[0180] 图 1 展示来自用各种剂量的 GS-7340 和 TDF 给药的患者的药物动力学数据。

[0181] 图 2 展示来自用各种剂量的 GS-7340 和 TDF 给药的患者的药物动力学数据。

[0182] 图 3A-B 展示来自用 GS-7340 的各种调配物给药的患者的药物动力学数据。

[0183] 图 4A-B 展示来自用 GS-7340 的各种调配物给药的患者的药物动力学数据。

[0184] 图 5A-B 展示来自用 GS-7340 的各种调配物给药的患者的药物动力学数据。

[0185] 图 6 展示来自用 GS-7340 的各种调配物给药的患者的药物动力学数据。

[0186] 图 7 展示来自用 GS-7340 的各种调配物给药的患者的药物动力学数据。

[0187] 图 8 展示来自用 GS-7340 的各种调配物给药的患者的药物动力学数据。

[0188] 图 9 展示来自用 GS-7340 的各种调配物给药的患者的药物动力学数据。

[0189] 图 10A-B 展示在经人 P- 糖蛋白基因 (Pgp ;MDR1) 和乳癌耐药蛋白 (BCRP) 基因转染的细胞中的底物分析的结果。

[0190] 图 11A-B 展示在经人 Pgp 和 BCRP 基因转染的细胞中的双向通透性分析的结果。

[0191] 图 12A-F 展示在经人 Pgp 和 BCRP 基因转染的细胞中的双向通透性分析的结果。

[0192] 图 13 展示替诺福韦艾拉酚胺半反丁烯二酸盐的 X 射线粉末衍射 (XRPD) 图案。

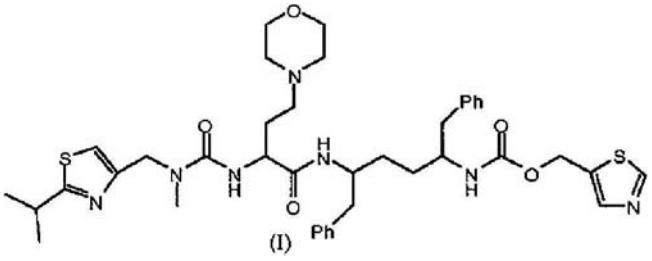
[0193] 图 14 展示替诺福韦艾拉酚胺半反丁烯二酸盐的 DSC 分析的图式。

[0194] 图 15 展示替诺福韦艾拉酚胺半反丁烯二酸盐的热解重量分析 (TGA) 数据的图式。

[0195] 图 16 展示替诺福韦艾拉酚胺半反丁烯二酸盐的动态气相吸附 (DVS) 分析的图式。

具体实施方式

[0196]



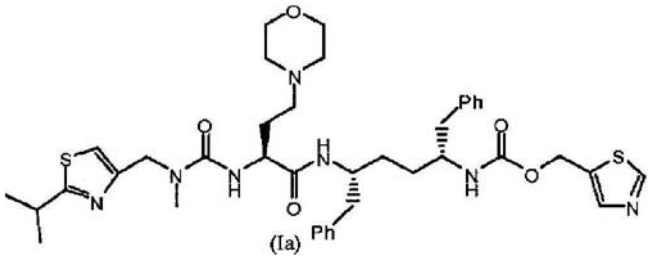
(I)

[0197] 可比西他 (化学名称 (2R,5R)-(5-{[(2S)-2-[(甲基 {[2-(丙 -2- 基)-1,3- 噻唑 -4- 基] 甲基 } 氨甲酰基) 氨基]]-4-(吗啉 -4- 基) 丁酰胺基 }-1,6- 二苯基己 -2- 基) 氨基甲酸 1,3- 噻唑 -5- 基甲酯) 是一种化学实体,其已展示为会不可逆抑制 CYP3A 酶的基于机制的抑制剂。

[0198] 进行详细的酶失活动力学研究,比较可比西他与利托那韦。已发现可比西他是人肝微粒体 CYP3A 活性的有效失活剂,其具有与利托那韦的动力学参数类似的动力学参数。另外,可比西他是 CYP2B6 的中度抑制剂 (效能与利托那韦类似)、CYP2D6 的弱抑制剂,且并不明显地抑制 CYP1A2、CYP2C8、CYP2C9、CYP2C19 或尿苷葡萄糖醛酸基转移酶 1A1。在异生物受体反式激活和人肝细胞研究中,可比西他并不展示 / 展示较弱的作为细胞色素 P450、UGT1A1 或 P- 糖蛋白的诱导剂 (在高达 30μM 下) 的潜力。通透性分析表明可比西他并非包括 P- 糖蛋白、MRP1 和 MRP2 的转运体的强底物或抑制剂。可比西他对肠道 P- 糖蛋白的抑制仅在归因于其较高水溶性的吸收期间是可能的,但其并未强到足以抑制在全身浓度下抑制转运体。这些数据指示,与利托那韦相比,可比西他是体外 CYP3A 的更具选择性的抑制剂和 CYP 酶的较弱诱导剂,其可潜在地引起与其它 CYP 酶的底物的更少的临床上显著相互作用。

[0199] 可比西他还可以富含式 (Ia) 立体异构体的组合物的形式存在 :

[0200]



(Ia)

[0201] 其为 (2R,5R)-5-((S)-2-(3-((2- 异丙基噻唑 -5- 基) 甲基)-3- 甲基脲基)-4- 吗啉代丁酰胺)-1,6- 二苯基己 -2- 基氨基甲酸噻唑 -5- 基甲酯。

[0202] 在一个实施例中,可比西他具有 85±5%式 (Ia) 立体异构体的富集浓度。在另一实施例中,可比西他具有 90±5%式 (Ia) 立体异构体的富集浓度。在另一实施例中,可比西他具有 95±2%式 (Ia) 立体异构体的富集浓度。在另一实施例中,可比西他具有 99±1%式 (Ia) 立体异构体的富集浓度。在另一实施例中,可比西他以纯式 (Ia) 立体异构体形式存在。

[0203] 可比西他与 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的共投与增强人中 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的全身暴露,改进 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的药物动力学 (包含 (但不限于)C_{max} 增大),且提高 GS-7340/ 替诺福韦艾拉酚胺半反丁烯二酸盐 / 替诺福韦的血液水平。因此,与可比西他共投与的 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐可以比先前认为会实现治疗性作用低的量投与。所述较低量可为在不存在可比西他共投与的情况下将为次治疗的量。

[0204] 在不受任何本发明的理论束缚的情况下,据相信,可比西他可起作用以抑制 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的肠道 Pgp 介导的肠道分泌。在体外研究中,可比西他和利托那韦显著增加经 P- 糖蛋白 (Pgp) 和乳癌耐药蛋白 (BCRP) 转染的细胞中的探针底物 (如钙黄绿素 AM 和 Hoechst33342) 的累积,且发现可比西他是这些转运体的底物。可比西他似乎是 Pgp 和 BCRP 的底物且很可能具有与共投与的药剂竞争的抑制模式。可比西他似乎是 Pgp 和 BCRP 的相对较弱抑制剂,且仅可在由可比西他在胃肠道中可实现的高溶解度和所得高浓度促进的肠道吸收期间对这些转运体具有瞬时作用。合起来,这些结果表明可比西他可有效抑制肠道转运体且增加共投与的底物 (包括 HIV 蛋白酶抑制剂和 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐) 的吸收,促成其作为药物增强剂的有效性。

[0205] 如本文所使用,术语“共给药”(或“共投与”) 是指在彼此 24 小时时期内投与两种或两种以上药剂,例如作为临床治疗方案的一部分。在其它实施例中,“共给药”是指在彼此 2 小时内投与两种或两种以上药剂。在其它实施例中,“共给药”是指在彼此 30 分钟内投与两种或两种以上药剂。在其它实施例中,“共给药”是指在彼此 15 分钟内投与两种或两种以上药剂。在其它实施例中,“共给药”是指同时投与两种或两种以上药剂,或者作为单一调配物的一部分或者作为利用相同或不同途径投与的多个调配物。

[0206] 术语“单位剂型”是指物理上个别单位,如胶囊、片剂或溶液,其适合作为单位剂量用于人类患者,每一单位含有经计算以产生治疗性作用的预定数量的一或多种活性成分以及至少一种医药学上可接受的稀释剂或载剂或其组合。单位剂量调配物含有活性成分的日剂量或单位日次剂量或其适当部分。

[0207] 术语化合物的“次治疗量”是在给药后不足以实现所需治疗效益的任何量的化合物。

[0208] 术语“增强量”或“增强剂量”是改进第二化合物的药物动力学（或增加可利用性或暴露）所需的化合物的量。增强量或增强剂量可改进第二化合物的药物动力学（或增加其可利用性或暴露）达到其在个体中具治疗性的水平。换句话说，次治疗量的第二化合物（即在未共投与增强量的情况下投与时的次治疗量）在个体中因在共投与增强量后改进的药物动力学（或增加的可利用性或暴露）而达到治疗性水平。

[0209] 本发明还提供一种用于治疗或防治疾病、病症和病况的方法。疾病、病症或病况的实例包括（但不限于）逆转录病毒感染或与逆转录病毒感染有关的疾病、病症或病况。逆转录病毒为 RNA 病毒且一般被归类为 α 逆转录病毒属、β 逆转录病毒属、δ 逆转录病毒属、ε 逆转录病毒属、γ 逆转录病毒属、慢病毒和泡沫病毒属家族。逆转录病毒的实例包括（但不限于）人类免疫缺陷病毒 (HIV)、人嗜 T 淋巴细胞病毒 (HTLV)、劳斯氏肉瘤病毒 (rous sarcoma virus ;RSV) 和禽白血病病毒。一般来说，逆转录病毒基因组的三种基因编码成熟病毒的蛋白质 :gag（基团特异性抗原）基因，其编码病毒的核心和结构蛋白质 ;pol（聚合酶）基因，其编码病毒的酶，包括逆转录酶、蛋白酶和整合酶 ;和 env（包膜）基因，其编码逆转录病毒表面蛋白质。

[0210] 逆转录病毒通过向宿主细胞中释放 RNA 和 pol 产物的复合物以及其它物质来附着并侵入宿主细胞。逆转录酶接着从病毒 RNA 产生双链 DNA。双链 DNA 被导入宿主细胞的核并通过病毒整合酶整合到宿主细胞基因组中。来自经整合的 DNA 的新生病毒在将经整合病毒 DNA 通过宿主细胞聚合酶转化成 mRNA 时形成，且病毒形成所必需的蛋白质通过病毒蛋白酶的作用产生。病毒粒子经历出芽且从宿主细胞释放以形成成熟病毒。

[0211] 活性剂可以任何常规方式投与人。虽然活性剂可作为原料化合物投与，但其优选地作为医药组合物投与。盐、载剂或稀释剂在与其它成分相容且对其接受者无害的意义上必须为可接受的。用于口服投药的载剂或稀释剂的实例包括玉米淀粉、乳糖、硬脂酸镁、滑石、微晶纤维素、硬脂酸、聚维酮、交联聚维酮、磷酸氢钙、羟基乙酸淀粉钠、羟丙基纤维素（例如低取代的羟丙基纤维素）、羟丙基甲基纤维素（例如羟丙基甲基纤维素 2910) 和月桂基硫酸钠。

[0212] 医药组合物可以通过任何合适的方法来制备，如药学领域中熟知的那些方法，例如，如真纳罗 (Gennaro) 等人，《雷明顿药物科学》(Remington′ s Pharmaceutical Sciences)（第 18 版，马克出版公司 (Mack Publishing Company)，1990)，尤其第 8 部分 :医药制剂和其制造 (Pharmaceutical preparations and their Manufacture) 中所述的方法的方法。所述方法包括将 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐与载剂或稀释剂和任选地一或多种附加成分相关的步骤。所述附加成分包括在此项技术中常规的那些成分，如填充剂、粘合剂、赋形剂、崩解剂、润滑剂、著色剂、调味剂、甜味剂、防腐剂（例如抗微生物防腐剂）、悬浮剂、增稠剂、乳化剂和 / 或润湿剂。

[0213] 术语“GS-7340”或其医药学上可接受的盐等包括其任何非晶形、结晶、共结晶、络合或其它物理形式。在一个实施例中，投与包含医药学上可接受的共形成物和 GS-7340 的组合物。医药学上可接受的共形成物可为能够与 GS-7340 一起形成“医药学上可接受的盐”的任何医药学上可接受的化合物。举例来说，医药学上可接受的共形成物可为医药学上可接受的酸（例如己二酸、L- 天冬氨酸、柠檬酸、反丁烯二酸、顺丁烯二酸、苹果酸、丙二酸、丁二酸、酒石酸或草酸）。在本发明的一个实施例中，医药学上可接受的共形成物是二酸。在

另一实施例中，医药学上可接受的共形成物是反丁烯二酸。在另一实施例中，可投与包含比率为约 0.5±0.05 的共形成物和 GS-7340 的组合物。GS-7340 的一种形式是半反丁烯二酸盐形式（替诺福韦艾拉酚胺半反丁烯二酸盐），如本文中进一步所述。

[0214] 医药组合物可提供药剂（例如 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐）在一段时间内的控制、缓慢释放或持续释放。药剂（例如 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐）的控制、缓慢释放或持续释放与在常规调配物情况下相比可将药剂在人的血流中维持更长时间段。医药组合物包括（但不限于）包衣的片剂、球粒、溶液、粉末、胶囊以及 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐在不溶于生理体液的介质中的分散液，或其中治疗性化合物在医药组合物因机械、化学或酶活性而降解之后释放。

[0215] 本发明的医药组合物可例如呈丸剂、胶囊、溶液、粉末或片剂形式，其各自含有预定量的 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐。在本发明的一个实施例中，医药组合物呈包含 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的片剂形式。在本发明的另一实施例中，医药组合物呈包含 GS-7340 和本文中提供的实例中采用并描述的片剂的组分的片剂形式。

[0216] 对于口服投药，精细粉末或颗粒可含有稀释剂、分散剂和 / 或表面活性剂且可例如存在于以下各项中 ：水或糖浆、呈无水状态的胶囊或药囊、或其中可包括悬浮剂的非水性溶液或悬浮液、或其中可包括粘合剂和润滑剂的片剂。

[0217] 在以液体溶液或悬浮液形式投与时，调配物可含有 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐和纯化水。液体溶液或悬浮液中任选的组分包括合适的甜味剂、调味剂、防腐剂（例如抗微生物防腐剂）、缓冲剂、溶剂和其混合物。调配物的组分可提供一种以上功能。举例来说，合适的缓冲剂还可充当调味剂以及甜味剂。

[0218] 合适的甜味剂包括例如糖精钠、蔗糖和甘露糖醇。可使用两种或两种以上甜味剂的混合物。甜味剂或其混合物通常以总组合物的约 0.001 重量％到约 70 重量％的量存在。合适的调味剂可存在于医药组合物中以提供樱桃风味、棉花糖风味或其它合适的风味，从而使医药组合物更容易为人摄取。调味剂或其混合物通常以总组合物的约 0.0001 重量％到约 5 重量％的量存在。

[0219] 合适的防腐剂包括例如对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、苯甲酸钠和苯扎氯铵。可使用两种或两种以上防腐剂的混合物。防腐剂或其混合物通常以总组合物的约 0.0001 重量％到约 2 重量％的量存在。

[0220] 合适的缓冲剂包括例如柠檬酸、柠檬酸钠、磷酸、磷酸钾和各种其它酸和盐。可使用两种或两种以上缓冲剂的混合物。缓冲剂或其混合物通常以总组合物的约 0.001 重量％到约 4 重量％的量存在。

[0221] 用于液体溶液或悬浮液的合适溶剂包括例如山梨糖醇、丙三醇、丙二醇和水。可使用两种或两种以上溶剂的混合物。溶剂或溶剂系统通常以总组合物的约 1 重量％到约 90 重量％的量存在。

[0222] 医药组合物可与佐剂共投与。举例来说，非离子表面活性剂（如聚氧乙烯油醇醚和正十六烷基聚乙烯醚）可与医药组合物一起投与或并入医药组合物中，从而人工地增加肠道壁的通透性。酶促抑制剂也可与医药组合物一起投与或并入医药组合物中。

[0223] GS-7340

[0224] 在本发明的一个实施例中，投与剂量 3mg、3±2mg 或 3±1mg 的 GS-7340 或其医药学上可接受的盐。

[0225] 在本发明的一个实施例中，投与剂量 8±3mg、8±2mg 或 8±1mg 的 GS-7340 或其医药学上可接受的盐。

[0226] 在本发明的一个实施例中，单位剂型包含剂量 8±2mg 的 GS-7340 或其医药学上可接受的盐。

[0227] 在本发明的各种实施例中，投与剂量 8±3mg、25±10mg、10±5mg、25±5mg、25±2mg、40±10mg、40±5mg、40±2mg、60±20mg、60±10mg、100±20mg、100±10mg、125±20mg、125±10mg、150±20mg、150±10mg、200±40mg 或 200±15mg 的 GS-7340 或其医药学上可接受的盐。

[0228] 所需日剂量的 GS-7340 还可以在全天适当时间间隔下单独投与的两个、三个、四个、五个、六个或六个以上次剂量形式（任选地呈单位剂量形式）投与。

[0229] 血流中替诺福韦 /GS-7340 的浓度可以血浆浓度（例如 ng/mL）形式测量。用于测定血浆浓度的药物动力学参数包括（但不限于）观察到的最大血浆浓度 (C_{max})、在给药间隔结束时观察到的血浆浓度或“谷”浓度 (C_{τ} 或 C_{min})、从时间零点直到最后一个可定量时间点的血浆浓度时间曲线下面积 (AUC)($AUC_{0-最后}$)、从时间零点到无限的 AUC(AUC_{0-inf})、给药间隔内的 AUC(AUC_{τ})、在投与后观察到的最大血浆浓度的时间 (t_{max}) 以及血浆中 GS-7340 的半衰期 ($t_{1/2}$)。

[0230] 根据本发明方法与食物一起投与 GS-7340 还可增加 GS-7340 的吸收。GS-7340 的吸收可通过在投与 GS-7340 之后随时间推移血流中达到的浓度来测量。通过与食物一起投与 GS-7340 使吸收增加还可通过如与当 GS-7340 在无食物情况下投与时的值相比 GS-7340 的 C_{max} 和 / 或 AUC 增加来证明。通常，蛋白酶抑制剂与食物一起投与。

[0231] 替诺福韦艾拉酚胺半反丁烯二酸盐

[0232] 在一个实施例中，提供替诺福韦艾拉酚胺的半反丁烯二酸盐形式（即替诺福韦艾拉酚胺半反丁烯二酸盐）。此形式的反丁烯二酸与替诺福韦艾拉酚胺之比（即化学计量比或摩尔比）可以是 0.5±0.1、0.5±0.05、0.5±0.01 或约 0.5、或其类似比值。

[0233] 在一个实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐由反丁烯二酸与替诺福韦艾拉酚胺以 0.5±0.1 之比组成。

[0234] 在一个实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐主要由反丁烯二酸与替诺福韦艾拉酚胺以 0.5±0.1 之比组成。

[0235] 在一个实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐的 XRPD 图案的 2θ 值包含 6.9±0.2°、8.6±0.2°、10.0±0.2°、11.0±0.2°、12.2±0.2°、15.9±0.2°、16.3±0.2°、20.2±0.2° 和 20.8±0.2°。

[0236] 在一个实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐的 XRPD 图案包含至少四个 2θ 值，所述 2θ 值选自 6.9±0.2°、8.6±0.2°、10.0±0.2°、11.0±0.2°、12.2±0.2°、15.9±0.2°、16.3±0.2°、20.2±0.2° 和 20.8±0.2°。

[0237] 在一个实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐的 DSC 起始吸热线是 131±2℃或 131±1℃。

[0238] 在各种实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐组合物包含少于约 5 重

量%、1 重量%或 0.5 重量%的替诺福韦艾拉酚胺单反丁烯二酸盐。

[0239] 在一个实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐组合物包含不可检测到的替诺福韦艾拉酚胺单反丁烯二酸盐。

[0240] 替诺福韦艾拉酚胺（即化合物 9-[(R)-2-[[(S)-[[(S)-1-（异丙氧基羰基）乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤）可如美国专利第 7,390,791 号中所述制备。

[0241] 在本发明的各种实施例中，剂量 3mg、3±2mg、3±1mg、8±3mg、8±2mg、8±1mg、

[0242] 在本发明的一个实施例中，单位剂型包含剂量 8±2mg 的替诺福韦艾拉酚胺半反丁烯二酸盐。

[0243] 25±10mg、10±5mg、10mg、25±5mg、25±2mg、40±10mg、40±5mg、40±2mg、60±20mg、60±10mg、100±20mg、100±10mg、125±20mg、125±10mg、150±20mg、150±10mg、200±40mg 或 200±15mg 的替诺福韦艾拉酚胺半反丁烯二酸盐被投与。

[0244] 所需日剂量的替诺福韦艾拉酚胺半反丁烯二酸盐还可以在全天适当时间间隔下单独投与的两个、三个、四个、五个、六个或六个以上次剂量形式（任选地呈单位剂量形式）投与。

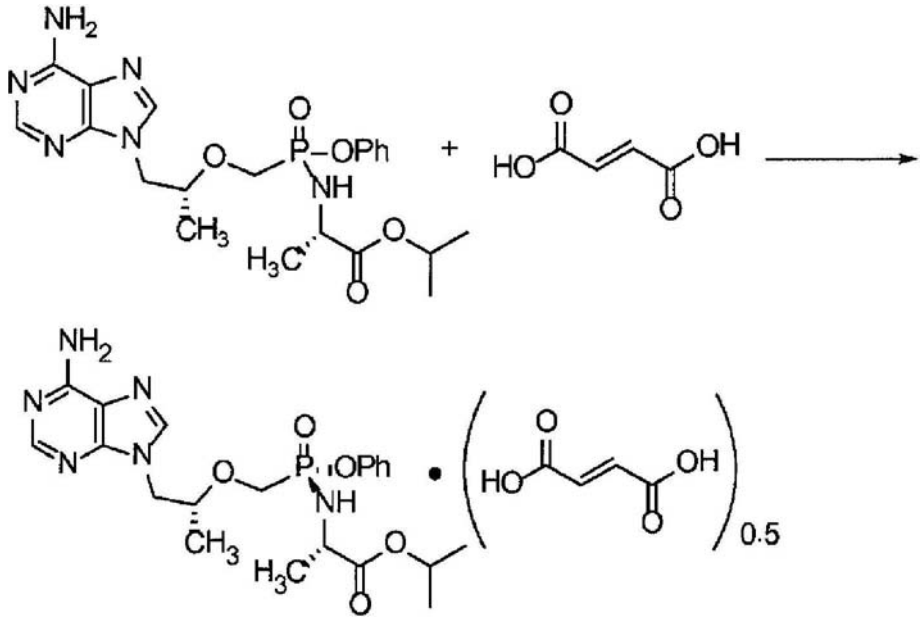
[0245] 血流中替诺福韦、GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的浓度可以血浆浓度（例如 ng/mL）形式测量。用于测定血浆浓度的药物动力学参数包括（但不限于）观察到的最大血浆浓度（C_{max}）、在给药间隔结束时观察到的血浆浓度或“谷”浓度（C_{τ} 或 C_{min}）、从时间零点直到最后一个可定量时间点的血浆浓度时间曲线下面积（AUC）（$AUC_{0-最后}$）、从时间零点到无限的 AUC（AUC_{0-inf}）、给药间隔内的 AUC（AUC_{τ}）、在投与后观察到的最大血浆浓度的时间（t_{max}）以及血浆中替诺福韦、GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的半衰期（$t_{1/2}$）。

[0246] 根据本发明方法与食物一起投与 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐还可增加 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的吸收。GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的吸收可通过在投与 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐之后随时间推移血流中达到的浓度来测量。通过与食物一起投与 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐使吸收增加还可通过如与当 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐在无食物情况下投与时的值相比 GS-7340 或替诺福韦艾拉酚胺半反丁烯二酸盐的 C_{max} 和 / 或 AUC 增加来证明。通常，蛋白酶抑制剂与食物一起投与。

[0247] 选择性结晶 - 替诺福韦艾拉酚胺半反丁烯二酸盐

[0248] 在一个实施例中，可以使用选择性结晶来制备替诺福韦艾拉酚胺半反丁烯二酸盐。此制备方法流程的实例如下。

[0249]



[0250] 可以通过使包含 :a) 合适的溶剂 ;b) 反丁烯二酸 ;c) 替诺福韦艾拉酚胺 ;和任选地 d) 一或多个包含替诺福韦艾拉酚胺半反丁烯二酸盐的晶种的溶液经受供反丁烯二酸与替诺福韦艾拉酚胺结晶的条件来执行所述方法。起始溶液可以含有替诺福韦艾拉酚胺的单一非对映异构体或替诺福韦艾拉酚胺和其其它非对映异构体中的一或多种 (例如美国专利第 7,390,791 号中所描述的 GS-7339) 的混合物。

[0251] 选择性结晶可在任何合适的溶剂中进行。举例来说,其可在质子溶剂或非质子性有机溶剂或其混合物中进行。在一个实施例中,溶剂包含质子溶剂 (例如水或异丙醇)。在另一实施例中,溶剂包含非质子有机溶剂 (例如丙酮、乙腈 (ACN)、甲苯、乙酸乙酯、乙酸异丙酯、庚烷、四氢呋喃 (THF)、2- 甲基 THF、甲基乙基酮或甲基异丁基酮、或其混合物)。在一个实施例中,溶剂包含 ACN 或 ACN 与最多约 50% 氯化甲烷 (按体积计) 的混合物。选择性结晶也可以在任何合适的温度 (举例来说,介于约 0℃到约 70℃范围内的温度) 下进行。在一个特定实施例中,拆分在约 0℃的温度下进行。

[0252] 替诺福韦艾拉酚胺的半反丁烯二酸盐形式相对于单反丁烯二酸盐形式的一个主要优势是其清除 GS-7339(即 9-[(R)-2-[[(R)-[[(S)-1-(异丙氧基羰基) 乙基] 氨基] 苯氧基氧膦基] 甲氧基] 丙基] 腺嘌呤 ;描述于例如美国专利第 7,390,791 号中) 的出色能力,GS-7339 是有效医药成分中的主要非对映异构杂质。因此,替诺福韦艾拉酚胺的半反丁烯二酸盐形式可以比单反丁烯二酸盐形式更容易且简单地与杂质分离。替诺福韦艾拉酚胺半反丁烯二酸盐相对于单反丁烯二酸盐形式的其它主要优点包括改进的热力学和化学稳定性 (包括长期储存稳定性)、优良的方法再现性、优良的药品含量均一性和较高熔点。

[0253] 替诺福韦艾拉酚胺半反丁烯二酸盐适用于治疗和 / 或防治人或动物中的一或多种病毒感染,包括由 DNA 病毒造成的感染、RNA 病毒、疱疹病毒 (例如 CMV、HSV1、HSV2、VZV)、逆转录病毒、肝炎病毒 (例如 HBV)、乳头瘤病毒、汉坦病毒、腺病毒和 HIV。美国专利第 6,043,230 号 (以全文引用的方式并入本文中) 和其它公开案描述核苷酸类似物 (如替诺福韦酯) 的抗病毒特异性。如替诺福韦酯,替诺福韦艾拉酚胺是替诺福韦的另一前药形式,且可以用于治疗和 / 或防治相同病况。

[0254] 替诺福韦艾拉酚胺半反丁烯二酸盐可以通过对待治疗病况来说适当的任何途径

来加以投与。合适的途径包括口服、经直肠、经鼻、局部（包括眼部、颊内和舌下）、经阴道和肠胃外（包括皮下、肌肉内、静脉内、皮内、鞘内和硬膜外）。一般来说，替诺福韦艾拉酚胺半反丁烯二酸盐经口投与，但其可以通过本文提到的任何其它途径来加以投与。

[0255] 相应地，医药组合物包括适合于局部或全身性投与（包括口服、经直肠、经鼻、颊内、舌下、经阴道或肠胃外（包括皮下、肌肉内、静脉内、皮内、鞘内和硬膜外）投与的那些医药组合物。）调配物呈单位剂型形式，并且通过在药学领域中熟知的任何方法来加以制备。

[0256] 对口服治疗性投与来说，替诺福韦艾拉酚胺半反丁烯二酸盐可以与一或多种赋形剂组合，并且以可吞食片剂、颊内片剂、糖衣片、胶囊、酏剂、悬浮液、糖浆、粉片等等形式加以使用。所述医药组合物和制备将通常含有至少0.1％替诺福韦艾拉酚胺半反丁烯二酸盐。此活性化合物在组合物和制剂中的百分比当然可以变化，并且宜可以介于指定单位剂型重量的约2％到约60％之间或更多。活性化合物在所述治疗学上适用的医药组合物中的量优选地可以使得在投与单一单位剂量（例如片剂）之后将获得有效剂量浓度。其它剂量调配物在反复投与亚临床有效量的替诺福韦艾拉酚胺半反丁烯二酸盐之后，可以提供治疗学上有效量的替诺福韦艾拉酚胺半反丁烯二酸盐。优选的单位剂量调配物包括含有日剂量（例如单一日剂量）替诺福韦艾拉酚胺半反丁烯二酸盐的那些调配物、以及含有单位每日亚临床剂量替诺福韦艾拉酚胺半反丁烯二酸盐或其适当部分（例如多次日剂量）的那些调配物。

[0257] 适合于口服投药的医药组合物可以表现为个别的单元（如胶囊、扁胶剂或片剂，其各自含有预定量的替诺福韦艾拉酚胺半反丁烯二酸盐）；粉末或颗粒；水性液体或非水性液体中的溶液或悬浮液；或水包油液体乳液或油包水液体乳液。替诺福韦艾拉酚胺半反丁烯二酸盐还可以表现为大丸剂、舐剂或糊状物。

[0258] 替诺福韦艾拉酚胺半反丁烯二酸盐优选地作为医药组合物或调配物的一部分来加以投与。这类医药组合物或调配物包含替诺福韦艾拉酚胺半反丁烯二酸盐以及一或多种医药学上可接受的载剂/赋形剂，并且任选地包含其它治疗成分。赋形剂/载剂在与调配物的其它成分相容且对患者并不有害的意义上必须是“可接受的”。赋形剂包括（但不限于）可以充当替诺福韦艾拉酚胺半反丁烯二酸盐媒剂或介质的物质（例如稀释用载剂）。其可以被封入硬或软壳明胶胶囊中，可以被压缩为片剂，或可以直接并入患者膳食的食物中。

[0259] 相应地，片剂、糖衣片、丸剂、胶囊等等还可以含有（但不限于）以下：粘合剂，如羟丙基纤维素、聚维酮或羟丙基甲基纤维素；填充剂，如微晶纤维素、预胶凝化淀粉、淀粉、甘露糖醇或单水合乳糖；崩解剂，如交联羧甲纤维素钠、交联聚维酮或羟基乙酸淀粉钠；润滑剂，如硬脂酸镁、硬脂酸或其它金属硬脂酸盐；甜味剂，如蔗糖、果糖、乳糖或阿斯巴甜糖；和/或调味剂，如胡椒薄荷、冬青油或樱桃调味剂。当单位剂型是胶囊时，除以上类型的材料之外，其可以含有液体载剂，如植物油或聚乙二醇。各种其它材料可以作为包衣存在或以其它方式改变固体单位剂型的物理形式。举例来说，片剂、丸剂或胶囊可以用明胶、聚合物、蜡、虫胶或糖等等包覆。当然，用于制备任何单位剂型的任何物质在所采用的量下通常将是医药学上可接受且实质上无毒的。另外，替诺福韦艾拉酚胺半反丁烯二酸盐可并入持续释放制剂和装置中。

[0260] 用于眼睛或其它外部组织（例如嘴部和皮肤）的感染时，医药组合物优选地以含有替诺福韦艾拉酚胺半反丁烯二酸盐的局部软膏或乳膏形式施用，其中替诺福韦艾拉酚胺

半反丁烯二酸盐的量是例如 0.01％到 10％ w/w（包括范围介于 0.1％与 5％之间且增量是 0.1％ w/w 的活性成分，如 0.6％ w/w、0.7％ w/w 等），优选地是 0.2％到 3％ w/w，且最优选地是 0.5％到 2％ w/w。当被调配为软膏时，活性成分可以与石蜡或可与水可混溶的软膏基质一起使用。或者，活性成分可以与水包油乳膏基质一起调配为乳膏。

[0261] 适合于在口内局部投与的医药组合物包括在调味基质（例如蔗糖和阿拉伯胶或黄芪胶）中包含替诺福韦艾拉酚胺半反丁烯二酸盐的口含片；在惰性基质（如明胶和甘油、或蔗糖和阿拉伯胶）中包含活性成分的片剂；和在合适液体载剂中包含活性成分的漱口剂。

[0262] 用于经直肠投与的调配物可以表现为具有包含例如可可油或水杨酸酯的合适基质的栓剂。

[0263] 适合于肠胃外投与的医药调配物为无菌的，并且包括可以含有抗氧化剂、缓冲剂、抑菌剂和使调配物与既定接收者血液等渗的溶质的水性与非水性注射溶液；和可以包括悬浮剂和增稠剂的水性与非水性无菌悬浮液。调配物可以表现为单位剂量或多剂量容器（例如具有弹性体塞子的密封安瓿和小瓶），并且可以在经冷冻干燥的（冻干）条件下储存，在使用之前仅需要即时加入无菌液体载剂（例如用于注射的水）即可。注射溶液和悬浮液可以从先前所描述的种类的无菌粉末、颗粒和片剂来制备。

[0264] 除尤其上述成分之外，医药组合物 / 调配物可以包括关于所讨论调配物类型的本领域中常规的其它成分。

[0265] 在另一实施例中，提供包含替诺福韦艾拉酚胺半反丁烯二酸盐以及所对应兽医学载剂的兽医学组合物。兽医学载剂是适用于向猫、狗、马、兔和其它动物投与组合物这一目的的材料，并且可以是在兽医学技术中呈以其它方式惰性或可接受并且与活性成分相容的固体、液体或气体材料。这些兽医学组合物可以口服、肠胃外或通过任何其它所需途径来投与。

[0266] 替诺福韦艾拉酚胺半反丁烯二酸盐可以用于提供含有基质或吸收剂材料和本发明活性成分的控制释放医药调配物，其中活性成分的释放可以受到控制与调节以允许较不频繁的给药或改进化合物的药物动力学或毒性概况。其中个别单元包含本发明化合物的适合于口服投药的控制释放调配物可以根据常规方法来加以制备。

[0267] 可以通过比较体外活性和动物模型中的体内活性来测定替诺福韦艾拉酚胺半反丁烯二酸盐的适用剂量。从小鼠和其它动物中的有效量 / 剂量外推人类中治疗学上有效量 / 剂量的方法是此项技术中已知的。

[0268] 用于治疗所需的替诺福韦艾拉酚胺半反丁烯二酸盐的量将因若干因素而变化，所述因素包括（但不限于）投与途径、所治疗病况的性质和患者的年龄与情况；最终，投与量将由值班医生或临床医生的诊断确定。替诺福韦艾拉酚胺半反丁烯二酸盐的治疗有效量 / 剂量至少取决于所治疗病况的性质、任何毒性或药物相互作用问题、化合物是用于防治（例如有时需要较低剂量）还是针对发作中的疾病或病况、输送的方法和医药调配物，并且将由临床医生使用常规剂量递增研究来测定。

[0269] 在一个实施例中，替诺福韦艾拉酚胺半反丁烯二酸盐的口服剂量可以介于每天每千克体重约 0.0001 到约 100mg，例如每天每千克体重约 0.01 到约 10mg，每天每千克体重约 0.01 到约 5mg，每天每千克体重约 0.5 到约 50mg，每天每千克体重约 1 到约 30mg，每天每

千克体重约 1.5 到约 10mg，或每天每千克体重约 0.05 到约 0.5mg 的范围内。作为一个非限制性实例，约 70kg 体重的成人的每日候选剂量将介于约 0.1mg 到约 1000mg、或约 1mg 到约 1000mg、或约 5mg 到约 500mg、或约 1mg 到约 150mg、或约 5mg 到约 150mg、或约 5mg 到约 100mg、或约 10mg 范围内，并且可呈单一或多个剂量形式。在一个实施例中，口服剂量的替诺福韦艾拉酚胺半反丁烯二酸盐可呈药剂的组合形式（例如替诺福韦艾拉酚胺半反丁烯二酸盐 / 恩曲他滨 / 埃替格韦 / 可比西他）。

[0270] 本文所描述的医药组合物可以进一步包括一或多种除替诺福韦艾拉酚胺半反丁烯二酸盐之外的治疗剂。在本发明的一个特定实施例中，所述另外的治疗剂可以选自由以下组成的群组 :HIV 蛋白酶抑制化合物、HIV 逆转录酶的非核苷抑制剂、HIV 逆转录酶的核苷抑制剂、HIV 逆转录酶的核苷酸抑制剂、HIV 整合酶抑制剂和 CCR5 抑制剂。

[0271] 治疗方法包括向需要替诺福韦艾拉酚胺半反丁烯二酸盐作为治疗性或预防性治疗的个体 / 患者投与替诺福韦艾拉酚胺半反丁烯二酸盐。因此，替诺福韦艾拉酚胺半反丁烯二酸盐可以向患有医学病症的个体 / 患者投与或向可能患上所述病症的个体投与。普通技术人员应了解进行这类治疗是为了改善、预防、延迟、治愈病症（包括复发病症）的症状或一系列症状、和 / 或降低其严重性。还可以进行所述治疗以延长个体的存活时间，例如使之超出在不进行这类治疗的情况下所预期的存活时间。可用替诺福韦艾拉酚胺半反丁烯二酸盐治疗的医学病症包括本文中论述的那些医学病症，包括（但不限于）HIV 感染（包括（但不限于）HIV-1 和 HIV-2 感染 ;优选地 HIV-1 感染）和 HBV 感染。

[0272] 可比西他的调配物

[0273] 当可比西他或其医药学上可接受的盐与某些特定固体载剂粒子（例如二氧化硅衍生物）组合时，所得组合具有改进的物理性质。尽管可比西他的性质是吸湿的，但所得组合具有相对较低的吸湿性。此外，所得组合是自由流动的粉末，具有可比西他的高负载值、可接受的物理和化学稳定性、快速药物释放性质和极好的可压缩性。因此，所得组合可易于处理成固体剂型（例如片剂），其具有良好的药物释放性质、低片剂易脆性、良好的化学和物理稳定性以及低量的残余溶剂。本发明的组合物代表显著进步，其促进可比西他用于治疗病毒感染（如 HIV）的商业开发。

[0274] 可比西他可与任何合适的固体载剂组合，其条件是所得组合具有允许其比母体化合物更易于调配的物理性质。举例来说，合适的固体载剂包括高岭土、膨润土、锂蒙脱石、胶态硅酸镁铝、二氧化硅、三硅酸镁、氢氧化铝、氢氧化镁、氧化镁以及滑石。在本发明的一个实施例中，固体载剂可包含硅酸钙（如 ZEOPHARM）或铝偏硅酸镁（如 NEUSILIN）。如本文所使用，“装载”在固体载剂上包括（但不限于）涂布在孔隙中和固体载剂表面上的化合物。

[0275] 适用于本发明组合物的二氧化硅衍生物和用于制备所述二氧化硅衍生物的方法包括国际专利申请公开案第 WO03/037379 号和其中所引用文献中所描述的那些。尤其适用于本发明组合物和方法的特定二氧化硅材料是AEROPERL®300（烟雾状二氧化硅），其购自德国杜塞尔多夫的赢创德固赛公司 (Evonik Degussa AG，Dusseldorf，Germany)。还可使用与本文所述的二氧化硅材料具有类似物理和化学性质的其它材料。

[0276] 利托那韦

[0277] 利托那韦 (N-[(2S,3S,5S)-3- 羟基 -5-[(2S)-3- 甲基 -2-{[甲基 ({[2-(丙 -2- 基)-1,3- 噻唑 -4- 基] 甲基 }) 氨甲酰基] 氨基 } 丁酰胺]-1,6- 二苯基

己 -2- 基] 氨基甲酸 1,3- 噻唑 -5- 基甲酯) 被开发为逆转录病毒 (HIV) 蛋白酶的抑制剂 ;但是,其目前以与可比西他类似的方式用于抑制某些细胞色素 P450 蛋白酶 (具体来说 Cyp3A4) 的作用,由此允许与将通过单独投与药物所获得的相比用于治疗 HIV 的药物的更大循环水平。尽管 GS-7340、替诺福韦或替诺福韦艾拉酚胺半反丁烯二酸盐中没有一者明显由细胞色素 P450 蛋白酶代谢,但预期利托那韦可以可比西他用于增强 GS-7340、替诺福韦或替诺福韦艾拉酚胺半反丁烯二酸盐的循环水平的方式使用,从而改进 GS-7340、替诺福韦或替诺福韦艾拉酚胺半反丁烯二酸盐的药物动力学并实现如本文中所公开的可比西他的用途的其它优点。

[0278] 组合治疗

[0279] 本发明的化合物和方法还可与以下化合物中的任一者一起使用 :

[0280] 1) 安普那韦 (amprenavir)、阿扎那韦 (atazanavir)、夫沙那韦 (fosamprenavir)、茚地那韦 (indinavir)、洛匹那韦 (lopinavir)、利托那韦、奈非那韦 (nelfinavir)、沙喹那韦 (saquinavir)、替拉那韦 (tipranavir)、贝卡那韦 (brecanavir)、地瑞那韦 (darunavir)、TMC-126、TMC-114、莫折那韦 (mozenavir, DMP-450)、JE-2147(AG1776)、L-756423、RO0334649、KNI-272、DPC-681、DPC-684、GW640385X、DG17、GS-8374、PPL-100、DG35 和 AG1859 ;

[0281] 2)HIV 逆转录酶的非核苷抑制剂,例如卡普拉林 (capravirine)、乙米韦林 (emivirine)、地拉夫定 (delaviridine)、依法韦仑 (efavirenz)、奈维拉平 (nevirapine)、(+) 卡拉脑立德 A((+)calanolide A)、依曲韦林 (etravirine)、GW5634、DPC-083、DPC-961、DPC-963、MIV-150、和 TMC-120、TMC-278(利匹韦林)、BILR355BS、VRX840773、UK-453061 和 RDEA806 ;

[0282] 3)HIV 逆转录酶的核苷抑制剂,例如齐多夫定 (zidovudine)、恩曲他滨、去羟肌苷 (didanosine)、司他夫定 (stavudine)、扎西他滨 (zalcitabine)、拉米夫定 (lamivudine)、阿巴卡韦 (abacavir)、氨多索韦 (amdoxovir)、艾夫他滨 (elvucitabine)、阿洛夫定 (alovudine)、MIV-210、瑞夕弗 (racivir, ±- 恩曲他滨)、D-d4FC、叠氮膦 (phosphazide)、福齐夫定替酯 (fozivudine tidoxil)、阿立地滨 (apricitibine, AVX754)、GS-7340、KP-1461 和磷夫定酯 (fosalvudine tidoxil, 以前称为 HDP99.0003) ;

[0283] 4)HIV 逆转录酶的核苷酸抑制剂,例如反丁烯二酸替诺福韦酯和阿德福韦酯 (adefovir dipivoxil) ;

[0284] 5)HIV 整合酶抑制剂,例如姜黄素、姜黄素衍生物、菊苣酸、菊苣酸衍生物、3,5- 二咖啡酰奎尼酸、3,5- 二咖啡酰奎尼酸衍生物、金精三羧酸、金精三羧酸衍生物、咖啡酸苯乙酯、咖啡酸苯乙酯衍生物、酪氨酸磷酸化抑制剂、酪氨酸磷酸化抑制剂衍生物、槲皮素、槲皮素衍生物、S-1360、新特维尔 (zintevir, AR-177)、L-870812 和 L-870810、MK-0518(雷特格韦 (raltegravir)), 埃替格韦、BMS-538158、GSK364735C、BMS-707035、MK-2048 和 BA011 ;

[0285] 6)gp41 抑制剂,例如恩夫韦地 (enfuvirtide)、西夫韦他 (sifuvirtide)、FB006M 和 TRI-1144 ;

[0286] 7)CXCR4 抑制剂,例如 AMD-070 ;

[0287] 8) 穿入抑制剂,例如 SP01A ;

[0288] 9)gp120 抑制剂,例如 BMS-488043 或 BlockAide/CR ;

[0289] 10)G6PD 和 NADH- 氧化酶抑制剂,例如免疫素 (immunitin) ;

[0290] 11)CCR5 抑制剂,例如阿普纳维 (aplaviroc)、维克利诺 (vicriviroc)、马拉维若 (maraviroc)、PRO-140、INCB15050、PF-232798(辉瑞公司) 和 CCR5mAb004 ;

[0291] 12) 用于治疗 HIV 的其它药物,例如 BAS-100、SPI-452、REP9、SP-01A、TNX-355、DES6、ODN-93、ODN-112、VGV-1、PA-457(贝韦立马 (bevirimat))、阿普林津 (Ampligen)、HRG214、西妥林 (Cytolin)、VGX-410、KD-247、AMZ0026、CYT99007A-221HIV、DEBIO-025、BAY50-4798、MDX010(伊匹单抗 (ipilimumab))、PBS119、ALG889 和 PA-1050040(PA-040) ;

[0292] 13) 干扰素,例如聚乙二醇化 rIFN-α 2b、聚乙二醇化 rIFN-α 2a、rIFN-α 2b、rIFN-α 2a、组合 IFNα(干复津 (infergen))、酶蛋白 (feron)、瑞非隆 (reaferon)、intermaxα、r-IFN-β、干复津 + 阿克姆 (actimmune)、IFN-ω 与 DUROS、白蛋白干扰素 (albuferon)、洛克特仑 (locteron)、白蛋白干扰素 (Albuferon)、立比扶 (Rebif)、口服干扰素 α、IFNα-2bXL、AVI-005、PEG- 干复津和聚乙二醇化 IFN-β ;

[0293] 14) 病毒唑类似物,例如雷贝妥 (rebetol)、柯匹吉 (copegus)、韦拉咪定 (viramidine,他瑞韦林 (taribavirin)) ;

[0294] 15)NS5b 聚合酶抑制剂,例如 NM-283、伐洛比西他滨 (valopicitabine)、R1626、PSI-6130(R1656)、HCV-796、BILB1941、XTL-2125、MK-0608、NM-107、R7128(R4048)、VCH-759、PF-868554 和 GSK625433 ;

[0295] 16)NS3 蛋白酶抑制剂,例如 SCH-503034(SCH-7)、VX-950(特拉普韦 (telaprevir))、BILN-2065、BMS-605339 和 ITMN-191 ;

[0296] 17)α- 葡糖苷酶 1 抑制剂,例如 MX-3253(赛格西弗 (celgosivir))、UT-231B ;

[0297] 18) 保肝药,例如 IDN-6556、ME3738、LB-84451 和 MitoQ ;

[0298] 19)HCV 的非核苷抑制剂,例如,苯并咪唑衍生物、苯并 -1,2,4- 噻二嗪衍生物、苯丙氨酸衍生物、A-831、GS-9190 和 A-689 ;和

[0299] 20) 治疗 HCV 的其它药物,例如日达仙 (zadaxin)、硝唑尼特 (nitazoxanide)(艾林尼 (alinea))、BIVN-401(维洛斯塔 (virostat))、PYN-17(阿尔替雷 (altirex))、KPE02003002、阿迪隆 (actilon)(CPG-10101)、KRN-7000、西瓦塞 (civacir)、GI-5005、ANA-975、XTL-6865、ANA971、NOV-205、特瓦新 (tarvacin)、EHC-18、NIM811、DEBIO-025、VGX-410C、EMZ-702、AVI4065、巴维昔单抗 (Bavituximab)、欧卢酚迪 (Oglufanide) 和 VX-497(美泊地布 (merimepodib))。

[0300] 示例性组合 (包括 (但不限于) 单一片剂方案) 包括 (a) 恩曲他滨 / 地瑞那韦 / 可比西他 /GS-7340 ;(b) 恩曲他滨 / 地瑞那韦 / 可比西他 / 替诺福韦艾拉酚胺半反丁烯二酸盐 ;(c) 恩曲他滨 / 地瑞那韦 / 可比西他 / 反丁烯二酸替诺福韦酯 (TDF) ;(d) 恩曲他滨 / 埃替格韦 / 可比西他 /GS-7340 ;(e) 恩曲他滨 / 埃替格韦 / 可比西他 / 替诺福韦艾拉酚胺半反丁烯二酸盐 ;(f) 恩曲他滨 / 埃替格韦 / 可比西他 /TDF ;(g) 可比西他 /GS-7340 ;(h) 可比西他 / 替诺福韦艾拉酚胺半反丁烯二酸盐 ;和 (i) 可比西他 /TDF。上文所列的组合可含有各种剂量的组分药剂 ;作为非限制性实例,以上组合 (b) 可包括 200mg 恩曲他滨、800mg 地瑞那韦、150mg 可比西他和 10mg 替诺福韦艾拉酚胺半反丁烯二酸盐,且以上组合 (e) 可包括 200mg 恩曲他滨、150mg 埃替格韦、150mg 可比西他和 10mg 替诺福韦艾拉酚胺半反丁烯二酸盐。

[0301] 一个替代示例性组合是恩曲他滨和替诺福韦艾拉酚胺半反丁烯二酸盐。恩曲他滨和 TDF 的组合当前作为TRUVADA®出售。也参见美国专利申请公开案第 2004/0224916 号，其内容特此以全文引用的方式并入本文中。本发明提供恩曲他滨和替诺福韦艾拉酚胺半反丁烯二酸盐的组合。此组合可含有各种剂量的两种组分药剂；作为非限制性实例，此组合可包括 200mg 恩曲他滨和 10mg 替诺福韦艾拉酚胺半反丁烯二酸盐。

[0302] 一个另外的替代示例性组合是恩曲他滨、利匹韦林和替诺福韦艾拉酚胺半反丁烯二酸盐。恩曲他滨、利匹韦林（非核苷逆转录酶抑制剂）和 TDF 的组合当前作为COMPLERA®出售。本发明提供恩曲他滨、利匹韦林和替诺福韦艾拉酚胺半反丁烯二酸盐的组合。此组合可含有各种剂量的三种组分药剂；作为非限制性实例，此组合可包括 200mg 恩曲他滨、25mg 利匹韦林和 10mg 替诺福韦艾拉酚胺半反丁烯二酸盐。

[0303] 另一额外的替代示例性组合是 GS-9441 和替诺福韦艾拉酚胺半反丁烯二酸盐。GS-9441（逆转录酶抑制剂）和 GS-7340 的组合公开于美国专利申请公开案第 2009/0075939 号和美国专利第 8,354,421 号中，其各自内容特此以全文引用的方式并入本文中。本发明提供 GS-9441 和替诺福韦艾拉酚胺半反丁烯二酸盐的组合。此组合可含有各种剂量的两种组分药剂；作为非限制性实例，此组合可包括 5-1500mg GS-9441 和 10mg 替诺福韦艾拉酚胺半反丁烯二酸盐。

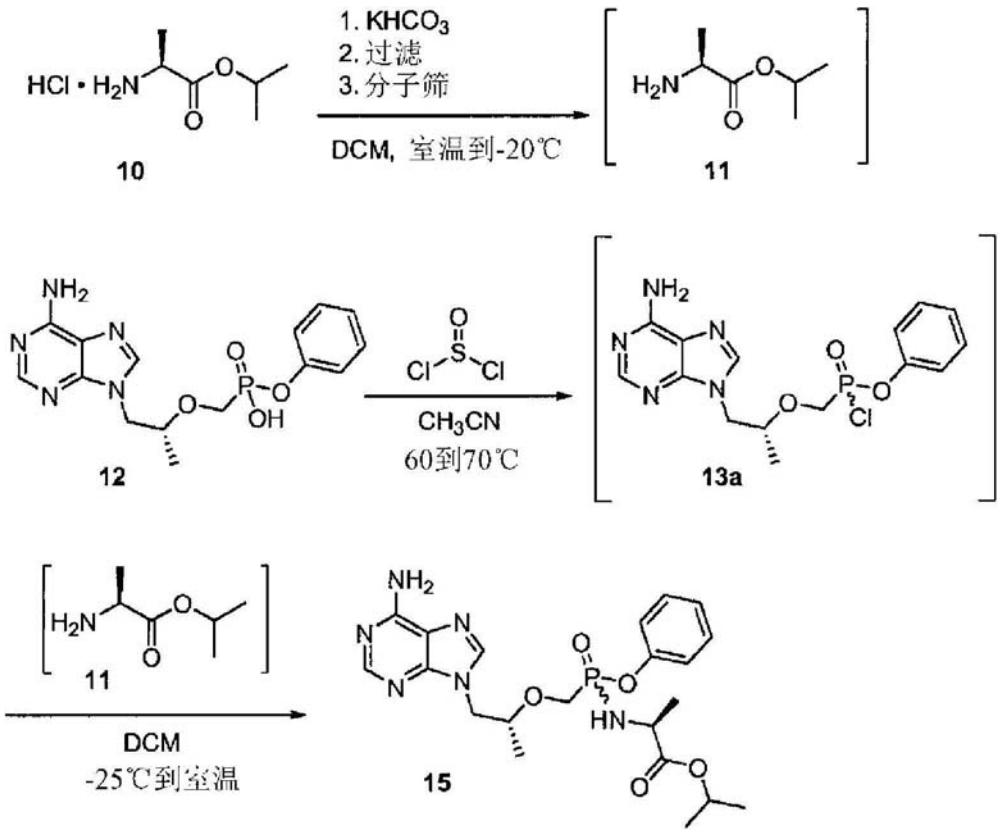
[0304] 各种组合中药剂的示例性量包括（但不限于）以下各项：(1) 可比西他：10-500mg、50-500mg、75-300mg、100-200mg 或 150mg；(2) 替诺福韦艾拉酚胺半反丁烯二酸盐：1-60mg、3-40mg、5-30mg、8-20mg 或 10mg；(3) 恩曲他滨：10-500mg、50-500mg、75-300mg、150-250mg 或 200mg；(4) 埃替格韦：10-500mg、50-500mg、75-300mg、100-200mg 或 150mg；(5) 地瑞那韦：300-1800mg、400-1600mg、500-1200mg、600-1000mg 或 800mg；和 (6) 利匹韦林：5-100mg、10-80mg、15-60mg、20-40mg 或 25mg。所属领域的技术人员将知道，就投与药剂的医药学上可接受的盐或络合物而论，所投与的量将相对于经加入以产生所述盐或络合物的组分的重量加以调节。

[0305] 现将通过以下非限制性实施例说明本发明。本文中提供的合成实例描述本发明化合物的合成以及用于制备本发明化合物的中间物。

[0306] 合成实例

[0307] 合成实例 1：制备 9-[(R)-2-[[(R,S)-1-[[(S)-（异丙氧基羰基）乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (15) 的非对映异构体混合物

[0308]



[0309] a. 制备化合物 11

[0310] 将 L- 丙氨酸异丙酯盐酸盐 10(1kg,5.97mol,1.0 当量）和碳酸氢钾 (1.45kg,14.5mol,2.43 当量）在最大搅拌下在 DCM(4kg) 中搅拌 10-14 小时，将罐温维持在 19 与 25℃之间。接着，过滤混合物且进一步用 DCM(2kg) 冲洗。滤液经4Å分子筛床干燥直到溶液的含水量≤ 0.05％为止。接着将含有化合物 11 的所得储备溶液冷却到 -20℃的罐温且保持以供进一步使用。

[0311] b. 制备化合物 13a

[0312] 在 60℃下经 2 小时以 10 个均等份向亚硫酰氯 (0.72kg,6.02mol,2.19 当量）于乙腈 (5.5kg) 中的溶液中加入化合物 12(1kg,2.75mol,1.00 当量）。接着，将罐温调节到 70℃，且搅拌 1-3 小时，直到根据 ^{31}P NMR 分析认为完成（目标 :在 12.6ppm 下的起始物质信号＞ 97.0％转化成在 22.0ppm 下的产物信号）为止。接着，将罐温调节到 40℃且施加真空。将混合物蒸馏到干燥，维持 40℃的最大夹套温度。干燥残余物接着吸收于二氯甲烷 (30kg) 中且将罐温调节到 19-25℃。保持含有化合物 13a 的所得浆料以供进一步使用。

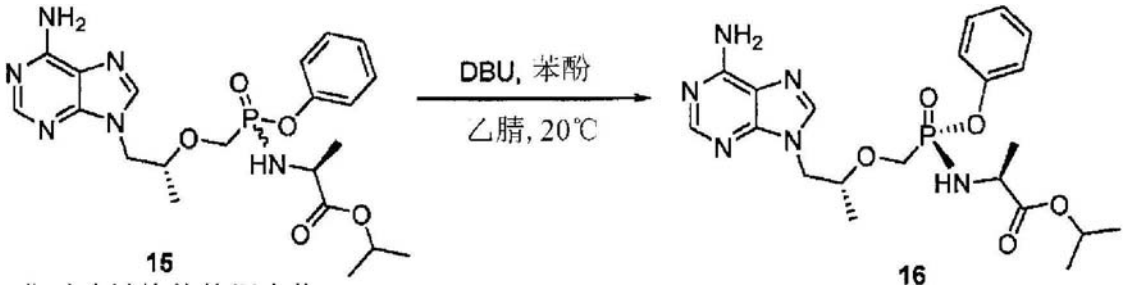
[0313] c. 制备化合物 15

[0314] 在 -25℃下经最少 2 小时向 L- 丙氨酸异丙酯 11(4.82 当量）的储备溶液中加入含有化合物 13a(1.0 当量）的浆料，维持罐温≤ -10℃。接着，将混合物保持在≤ -10℃的温度下持续至少 30 分钟，接着使用水润湿的 pH 纸进行 pH 值检查。如果 pH 值＜ 4，那么用三乙胺调节到 pH4-7。接着，将罐温调节到室温 (19-25℃）。在另一容器中，制备磷酸二氢钠 (2.2kg,18mol,6.90 当量）于水 (16kg) 中的溶液。将一半的磷酸二氢钠溶液馈入膦酸酰胺化物反应器中，且剧烈搅拌。使各层沉降并分配。有机层用剩余一半的磷酸二氢钠溶液再次洗涤。在另一容器中，制备碳酸氢钾 (1.1kg,11mol,4.22 当量）于水 (5.5kg) 中的溶液。将一半的碳酸氢钾溶液馈入有机相中，并剧烈搅拌。使各层沉降并分配。有机层依序用

剩余一半的碳酸氢钾溶液和最终水 (3.3kg) 洗液再次洗涤。接着,保留有机相并蒸馏到约 6L 的体积。分析所得溶液的含水量。如果含水量＞ 1.0%,那么可馈入 DCM 并重复蒸馏到约 6L。当溶液含水量低于或约为 1.0%时,将罐温调节到 19-25℃,随后排放含储备溶液的 DCM,得到 9-[(R)-2-[[(R,S)-1-[[(S)-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (15) 的非对映异构混合物。^{1}H NMR(400MHz,$CDCl_3$):δ 1.20-1.33(m,12H),3.62-3.74(m,1H),3.86-4.22(m,5H),4.30-4.44(m,1H),4.83-5.10(m,1H),6.02(brs,3H),7.18-7.34(m,5H),7.98-8.02(m,1H),8.32-8.36(m,1H);^{31}P NMR(162MHz,$CDCl_3$):δ.21.5,22.9。

[0315] 合成实例 2:对 9-[(R)-2-[[(R,S)-1-[[(S)-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (15) 的非对映异构混合物进行结晶诱导的动态拆分,得到 9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (16)

[0316]



[0317] (非对映异构体的混合物)

[0318] 将 22 重量% 9-[(R)-2-[[(R,S)-1-[[(S)-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (15) 的非对映异构混合物于乙腈中的溶液 (2.3kg 溶液,0.51kg15,1.1mol,1 当量)中馈入配备有顶置式搅拌器、蒸馏设备和氮气入口的容器中。通过在 100-300 毫巴下在 45℃ -55℃的温度范围内进行蒸馏将混合物浓缩到 30-35 重量%的最终浓度。接着去除蒸馏设备并且将溶液冷却到 20℃。利用 2.0%化合物 16 向溶液中加晶种并且在 20℃下搅拌一小时。加入苯酚 (9.9g,0.11mol,0.1 当量) 和 DBU(16g,0.11mol,0.1 当量),并且将混合物再搅拌 24 小时,或直到溶液中残留的化合物 16 的重量百分比小于 12%。接着将浆料冷却到 0℃并且在 0℃下再搅拌 18 小时。在 0℃下将浆料过滤并且用乙酸异丙酯:乙腈的 1 : 1 溶液 (1.5L) 洗涤。在 50℃真空烘箱中干燥固体,得到 0.40kg 呈白色固体状的化合物 16(80%产率)。^{1}H NMR(400MHz,$CDCl_3$):δ 1.21(m,9H),1.28(d,J = 7.0Hz,3H),3.65(dd,J = 13.1,10.7,1H)4.00(m,4H),4.33(dd,J = 14.4,3.1Hz,1H),5.00(m,1H)6.00(bs,2H),6.99(m,2H),7.07(m,1H),7.19(m,2H),7.97(s,1H),8.33(s,1H)。^{31}P NMR(162MHz,$CDCl_3$):δ.20.8。

[0319] 合成实例 3:以高非对映异构体纯度制备化合物 13a

[0320] 在环境温度下向化合物 12(10.0g,27.5mmol,1.00 当量)于甲苯 (60mL) 中的浆料中加入亚硫酰氯 (3.0mL,41mmol,1.5 当量)。将浆料加热到 70℃并且搅动 48-96 小时,直到根据 HPLC 认为反应和非对映异构体富集完成(目标:化合物 12 到化合物 13a 的转化率＞ 97.0%并且化合物 13a 的非对映异构体比＞ 90 : 10) 为止。通过真空蒸馏将混合物浓缩干燥,并且将干燥残余物吸收于甲苯 (50mL) 中。在环境温度下保持含有化合物 13a 的所

得浆料以供进一步使用。

[0321] 合成实例 4：以高非对映异构体纯度制备 9-[(R)-2-[[(R,S)-1-[[(S)-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (15)

[0322] 在 -25℃下经最少 45 分钟向 L- 丙氨酸异丙酯 11(4.50 当量) 于 DCM(80mL) 中的溶液中加入含有至少 90％非对映异构体纯的化合物 13a(1.00 当量) 于甲苯 (50mL) 中的浆料，内部温度维持≤ -20℃。接着，将混合物保持在≤ -20℃的温度下持续至少 30 分钟，并使用水润湿的 pH 纸进行 pH 值检查。如果 pH 值＜ 4，那么用三乙胺将其调节到 pH4-7。将罐温调节到室温 (19-25℃)。将混合物转移到分液漏斗并且依序用 10％ w/v 磷酸二氢钠水溶液 (2×50mL)、15％ w/v 碳酸氢钾水溶液 (2×20mL) 和水 (50mL) 洗涤。经无水硫酸钠干燥最终有机层，进行过滤并且在真空中浓缩成粘稠琥珀色油状物。将油状物溶解于甲苯 / 乙腈 (4 ： 1)(50mL) 中，并利用 9-[(R)-2-[[(R,S)-1-[[(S)-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (约 1mg，99 ： 1 非对映异构体比) 向溶液中加晶种并且在环境温度下搅拌 2 小时。将所得浆料过滤并用甲苯 / 乙腈 (4 ： 1)(15mL) 洗涤滤饼，并且在 40℃真空烘箱中干燥 16 小时，得到呈白色固体状的产物 9-[(R)-2-[[(R,S)-1-[[(S)-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤 (15)(10.0g，76.4％，97.5 ：2.5 非对映异构体比)。^{1}H NMR(400MHz，$CDCl_3$)：δ 1.20-1.33(m，12H)，3.62-3.74(m，1H)，3.86-4.22(m，5H)，4.30-4.44(m，1H)，4.83-5.10(m，1H)，6.02(brs，3H)，7.18-7.34(m，5H)，7.98-8.02(m，1H)，8.32-8.36(m，1H)；^{31}P NMR(162MHz，$CDCl_3$)：δ .21.5，22.9。

[0323] 合成实例 5：制备化合物 12

[0324] 将 PMPA(100.0g，0.35mol，1 当量) 馈入配备有顶置式搅拌器、回流冷凝器和氮气入口的容器中，之后馈入乙腈 (800mL)。向所述容器中加入三乙胺 (71.0g，0.70mol，2 当量)，之后添加 DMAP(42.6g，0.35mol，1 当量) 和亚磷酸三苯酯 (162.1g，0.52mol，1.5 当量)。将混合物加热到 80℃并且在 80℃下搅动≥ 48 小时或直到通过 ^{31}P NMR 确定反应完成为止。(直接从所述反应获取样品并且加入含有 10％ H_3PO_2 于 D_2O 中的插入物。所形成的中间物为 PMPA 酸酐并且在 6ppm 下；产物在 11ppm 下。当存在小于 5％的酸酐时，认为反应完成)。将反应混合物蒸馏到约 1.5 体积的乙腈并且用乙酸乙酯 (200mL) 和水 (300mL) 稀释。分离水层并且用乙酸乙酯 (200mL) 洗涤两次。将水层再次馈入容器中并且使用 12.1M HCl(21.0mL) 将 pH 值调节到 pH3。接着利用 0.05％化合物 12 向反应物中加晶种并且在 25℃下进行搅拌。经 20 分钟再加入 12.1M HCl(7.0mL) 直到实现 pH2 为止。在环境温度下将结晶搅拌 30 分钟并且接着经 2 小时冷却到 10℃。一旦达到 10℃，即在 10℃下将结晶搅拌 2.5 小时。将浆料过滤并用 pH1.5 水 (200g) 洗涤。在真空烘箱中干燥后，获得 102.2g 呈白色固体状的化合物 12(81％产率)。^{1}H NMR(400MHz，D_2O)：δ 1.31(d，J ＝ 6.1Hz，3H)，3.59(dd，J ＝ 14.0，9.0Hz，1H)，3.85(dd，J ＝ 14.0，9.0Hz，1H)，4.1(m，1H)，4.3(dd，J ＝ 15.0，9.0Hz，1H)，4.5(dd，J ＝ 15.0，2Hz，1H)，6.75(d，J ＝ 7Hz，2H)，7.15(t，J ＝ 7Hz，1H)，7.25(t，J ＝ 7Hz，2H)，8.26(s，1H)，8.35(s，1H)。^{31}P NMR(162MHz，D_2O)：δ .14.8。

[0325] 合成实例 - 替诺福韦艾拉酚胺半反丁烯二酸盐

[0326] 合成实例 6

[0327] 在 22 ℃ 下将替诺福韦艾拉酚胺单反丁烯二酸盐固体 (5.0g) 和

9-[(R)-2-[[(R)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤(GS-7339)单反丁烯二酸盐固体(0.75g)馈入35g MTBE中,并且搅拌混合物1小时。形成浆料,并且在旋转蒸发器中干燥。向固体中加入58g乙腈(ACN),并且将混合物加热到回流以溶解固体。使所得溶液在搅拌的同时下自然冷却。形成浆料,并且通过冰-水浴进一步冷却浆料。通过过滤分离固体,并且用5gACN洗涤。在真空烘箱中于40℃下干燥固体过夜。获得5.52g灰白色固体。通过XRPD来分析固体,并且发现其含有替诺福韦艾拉酚胺单反丁烯二酸盐、GS-7339单反丁烯二酸盐和替诺福韦艾拉酚胺半反丁烯二酸盐。

[0328] 合成实例7:经由选择性结晶制备替诺福韦艾拉酚胺半反丁烯二酸盐

[0329] 向反应器中馈入呈ACN中浆料形式的9-[(R)-2-[[[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤(9.7kg浆料,13.8重量%,1.0kg(2.10mol,1摩尔当量)9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤与0.35kg9-[(R)-2-[[(R)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤的非对映异构混合物),并且进一步用二氯甲烷(5kg)冲洗。在真空下且在夹套温度小于40℃下将混合物浓缩到约3L。随后在真空下且在夹套温度小于40℃下将浓缩物与ACN(6kg)共蒸发到约3L。用ACN(8.5kg)稀释浓缩物,并且升温到40℃-46℃。将温混合物过滤到第二反应器中,并且将滤液冷却到19℃-25℃。

[0330] 向以上溶液中依序馈入反丁烯二酸(0.13kg,1.12mol,0.542摩尔当量)和ACN(1kg),并且将混合物加热到67℃-73℃。借助精滤器将热混合物转移到反应器中,并且随后调整到54℃-60℃。加入替诺福韦艾拉酚胺的半反丁烯二酸盐形式的晶种晶体(5g)(举例来说,混合物可以用在合成实例6或后续生产中形成的替诺福韦艾拉酚胺半反丁烯二酸盐作为晶种),并且将所得混合物在54℃-60℃下搅拌约30分钟。经最少4小时将混合物冷却到0℃-6℃,并且随后在0℃-6℃下搅拌最少1小时。过滤所得浆料,并且用冷却的(0℃-6℃)ACN(2kg)冲洗。在真空下于45℃以下干燥产物,直到干燥损失(LOD)与有机挥发性杂质(OVI)极限相符合(LOD≤1.0%,二氯甲烷含量≤0.19%,乙腈含量≤0.19%),得到呈白色到灰白色粉末状的最终化合物,替诺福韦艾拉酚胺的半反丁烯二酸盐形式(典型产率是约0.95kg)。^{1}H NMR(400MHz,d6DMSO):δ1.06(d,J=5.6Hz,3H),1.12-1.16(m,9H),3.77(dd,J=10.4,11.6Hz,1H),3.84-3.90(m,2H),3.94(m,1H),4.14(dd,J=6.8,14.8Hz,1H),4.27(m,1H),4.85(七重峰,J=6.0Hz,1H),5.65(t,J=11.2Hz,1H),6.63(s,1H),7.05(d.J=7.6Hz,2H),7.13(t,J=7.2Hz,1H),7.24(s,2H),7.29(t,J=7.6Hz,2H),8.13(t,J=13.6Hz,2H),^{31}P NMR(162MHz,d6DMSO):δ23.3。

[0331] 合成实例8:制备替诺福韦艾拉酚胺半反丁烯二酸盐

[0332] 向配备有顶置式搅拌器的夹套反应器中馈入9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤(10g)、反丁烯二酸(1.22g)和ACN(100mL)。将混合物加热到70℃-75℃以溶解固体。通过经由筒式过滤器过滤来去除任何未溶解的粒子。将经过滤的溶液冷却到60℃-65℃,并且用1%(按重量计)替诺福韦艾拉酚胺半反丁烯二酸盐作为晶种进行结晶。使浆料老化30分钟,并且经2小时冷却到0℃-5℃。维持温度1-18小时,并且过滤所得浆料且用2mL冷ACN(0℃-5℃)洗涤。在真空下于50℃干燥固体,得到替诺福韦艾拉酚胺的半反丁烯二酸盐形式,如下文所描述对其

进行表征。

[0333] 对来自合成实例 8 的替诺福韦艾拉酚胺半反丁烯二酸盐的表征

[0334] 来自合成实例 8 的替诺福韦艾拉酚胺半反丁烯二酸盐由 9-[(R)-2-[[(S)-[[(S)-1-(异丙氧基羰基)乙基]氨基]苯氧基氧膦基]甲氧基]丙基]腺嘌呤和一半当量的反丁烯二酸组成。替诺福韦艾拉酚胺半反丁烯二酸盐是无水、不吸潮的，并且其 DSC 起始吸热线是约 131℃。

[0335] X 射线粉末衍射

[0336] 在以下实验设定中获得替诺福韦艾拉酚胺半反丁烯二酸盐的 XRPD 图案：45KV，45mA，Kα1=1.5406Å，扫描范围 2.° -40°，步长 0.0084°，计数时间：8.25 秒。替诺福韦艾拉酚胺半反丁烯二酸盐的 XRPD 图案显示在图 13 中。特征峰包括：6.9±0.2°、8.6±0.2°、10.0±0.2°、11.0±0.2°、12.2±0.2°、15.9±0.2°、16.3±0.2°、20.2±0.2° 和 20.8±0.2°。

[0337] 单晶 X 射线衍射

[0338] 晶体大小是 0.32×0.30×0.20mm^3。样品维持在 123K 下，并且使用波长为 0.71073Å的辐射源在 1.59° 到 25.39° 的 θ 范围中收集数据。单晶 X 射线衍射的条件和由此所收集的数据显示在表 1 中。

[0339] 表 1. 单晶 X 射线衍射

[0340]

经验式	$C_{23}H_{31}N_6O_7P$
式重	534.50
温度	123(2) K
晶体大小	0.32×0.30×0.20 mm^3
数据收集的 θ 范围	1.59°到 25.39°
波长	0.71073 Å
晶系	四方晶系

[0341]

空间群	P4(2)2(1)2	
单位晶胞尺寸	a = 18.1185(12) Å b = 18.1185(12) Å c = 17.5747(11) Å	α = 90° β = 90° γ = 90°
体积	5769.4(6) Å^3	
Z	8	
密度(计算值)	1.231 g/cm^3	

[0342] DSC 分析

[0343] 使用 2.517mg 替诺福韦艾拉酚胺半反丁烯二酸盐来进行 DSC 分析。以 10℃ / 分钟在 40℃ -200℃范围内对其进行加热。发现起始吸热线为约 131℃（图 14）。

[0344] TGA 数据

[0345] 使用 4.161mg 替诺福韦艾拉酚胺半反丁烯二酸盐来获得 TGA 数据。以 10℃ / 分钟在 25℃ -200℃范围内对其进行加热。样品在熔融之前损失 0.3 重量%（图 15）。确定其是无水形式。

[0346] DVS 分析

[0347] 使用 4.951mg 替诺福韦艾拉酚胺半反丁烯二酸盐来进行 DVS 分析。于 25℃下在氮气中在 10％到 90％相对湿度的湿度范围内保存材料；各步骤均持续 120 分钟以达到平衡。吸附等温线展示在图 16 中。发现材料是不吸潮的，并且在 90％相对湿度下吸收 0.65％水。

[0348] 清除非对映异构杂质

[0349] 在替诺福韦艾拉酚胺的先前合成中，主要杂质之一通常是非对映异构体 9-[(R)-2-[[(R)-[[(S)-1-(异丙氧基羰基）乙基］氨基］苯氧基氧膦基］甲氧基］丙基］腺嘌呤。与替诺福韦艾拉酚胺的单反丁烯二酸盐形式（描述于美国专利第 7,390,791 号中）相比，来自合成实例 8 的半反丁烯二酸盐形式具有清除此非对映异构杂质的出色能力。表 2（以下）中的数据展示替诺福韦艾拉酚胺半反丁烯二酸盐（批次 2）将非对映异构杂质清除到小于起始浓度的十分之一，而替诺福韦艾拉酚胺的单反丁烯二酸盐形式（批次 1）仅稍微清除所述非对映异构杂质。

[0350] 表 2. 清除能力比较

[0351]

批次	起始物质中的非对映异构杂质	溶剂	反丁烯二酸馈入(摩尔当量)	所获得的产物	产物中的非对映异构杂质
1	9.3%	ACN	0.9	单反丁烯二酸盐形式	7.6%
2	10.0%	ACN	0.5	半反丁烯二酸盐形式	0.65%

[0352] 化学稳定性

[0353] 比较替诺福韦艾拉酚胺的半反丁烯二酸盐形式与单反丁烯二酸盐形式的化学稳定性。如表 3（以下）中所示，在相同条件下，替诺福韦艾拉酚胺的半反丁烯二酸盐形式比单反丁烯二酸盐形式在化学上更稳定，并且展现更好的长期储存稳定性，降解（总降解产物％）明显更少。所评估的条件包括温度、相对湿度 (RH) 和容器封盖的开启或关闭状态。

[0354] 表 3. 化学稳定性比较

[0355]

储存条件	时间点(周)	单反丁烯二酸盐形式		半反丁烯二酸盐形式	
		TA*归一化面积%	总降解产物%	TA 归一化面积%	总降解产物%
40℃/75% RH 封盖关闭	0	97.1	0.69	98.4	0.05
	1	97.0	0.87	98.4	0.14
	2	96.6	1.18	98.5	0.14
	4	96.4	1.49	98.4	0.25
	8	95.4	2.36	98.0	0.49
40℃/75% RH 封盖打开	0	97.1	0.69	98.4	0.05
	1	96.9	0.90	98.5	0.15
	2	96.6	1.10	98.5	0.14
	4	96.2	1.67	98.4	0.26
	8	95.0	2.74	98.1	0.50
70℃ 封盖关闭	0	97.1	0.69	98.4	0.05
	2	96.2	1.83	98.5	0.22
	4	93.3	4.78	98.4	0.33

[0356] *TA 是替诺福韦艾拉酚胺

[0357] 热力学稳定性

[0358] 替诺福韦艾拉酚胺半反丁烯二酸盐的稳定形式筛选显示其在大多数溶剂（如ACN、甲苯、乙酸乙酯、甲基叔丁基醚(MTBE)、丙酮、THF和2-甲基THF)中是热力学上稳定的。单反丁烯二酸盐形式的类似稳定形式筛选显示此形式在以上所列的溶剂中不是热力学上稳定的。当悬浮于这些溶剂中时，替诺福韦艾拉酚胺的单反丁烯二酸盐形式在THF和2-甲基THF中完全转化为半反丁烯二酸盐形式，在ACN、乙酸乙酯、MTBE和丙酮中以及在环境温度下部分转化为半反丁烯二酸盐形式。

[0359] 热稳定性

[0360] 如由DSC数据所示，替诺福韦艾拉酚胺的半反丁烯二酸盐形式的熔点比单反丁烯二酸盐形式的熔点高约10℃，表明与单反丁烯二酸盐形式相比，半反丁烯二酸盐形式的热稳定性得到改进。

[0361] 生物学实例1：转运研究

[0362] Caco-2经上皮转运研究：使通道43与69之间的Caco-2细胞在24孔聚对苯二甲酸乙二醇酯(PET)transwell板（马萨诸塞州贝德福德的碧迪生物科学公司(BD Biosciences,Bedford,MA)）上经至少21天生长到汇合。实验使用获自生命技术公司(Life Technologies；纽约州格兰德岛(Grand Island)）的含有10mM HEPES和15mM葡萄糖的汉克氏缓冲盐溶液(Hank′s Buffered Salt Solution，HBSS)进行。将供体和接受体缓冲液的pH值分别调节到pH6.5和7.4。接受体孔使用补充有1％牛血清白蛋白的HBSS缓冲液。在测定转运抑制的研究中，将单层在分析缓冲液和抑制剂存在下预孵育60分钟以便使任何转运蛋白结合位点饱和。在预孵育之后，加入含有抑制剂和测试化合物的新鲜分析缓冲液。分析腔室中的测试化合物浓度通过耦接到串联质谱的液相色谱(LC/MS/MS)分析。测定经上皮电阻(TEER)和萤光黄渗透率以确保膜完整性。一式两份地进行每一个别的实验，且测定对照化合物阿替洛尔(atenolol；低渗透率）、普萘洛尔(propranolol；高渗透率）和长春花碱(vinblastine；外排转运）的渗透以满足每一批分析板的验收准则。

[0363] 经转染的马丁达比狗肾(Madin-Darby canine kidney，MDCKII)细胞中的Pgp和BCRP抑制分析：Pgp介导的转运的抑制是使用Pgp底物钙黄绿素AM和经人MDR1(ABCB1)基因（编码Pgp)转染的MDCKII细胞研究的。类似地，BCRP介导的转运的抑制是使用BCRP底物Hoechst33342和经人ABCG2基因（编码BCRP)转染的MDCKII细胞研究的。简言之，MDCKII细胞以5×10^4个细胞/孔的密度接种于具有透明底物的96孔黑色细胞培养板中且过夜生长到汇合。将测试化合物稀释于含有10μM Hoechst33342的细胞培养基中且与MDCKII-BCRP和未经转染的细胞一起孵育3小时。在去除含有Hoechst33342和测试化合物的培养基之后，用温热培养基洗涤细胞两次，且将其在室温下在含有20mM Tris-HCl(pH9.0)和0.4％Triton X-100的缓冲液中裂解5-10分钟。在353nm的激发波长和460nm的发射波长下分析各孔的Hoechst33342荧光。

[0364] 经转染的MDCKII细胞中的Pgp和BCRP底物分析：使MDCKII细胞在24孔PET transwell板（碧迪生物科学公司）上经4-6天生长到汇合。将相同缓冲液用于如上所述的供体和接受体孔以用于caco-2研究。如上所述针对caco-2经上皮转运研究进行实验且通过LC/MS/MS分析样品。使用与以上针对caco-2研究所述的质量控制和验收准则类似的质量控制和验收准则。测定萤光黄、阿替洛尔和普萘洛尔的TEER值和渗透率以满足每一批分析板的验收准则。针对模型Pgp底物长春花碱和BCRP底物哌唑嗪在经转染的单层对未

经转染的单层中测定外排比高至少 3 倍。

[0365] 数据分析：使用 GraphPad Prism5（加利福尼亚州圣地亚哥的图板软件公司 (GraphPad Software Inc.，San Diego，CA) 使用以变量希尔系数 (Hill coefficient) 使抑制对浓度拟合到 S 形曲线的非线性曲线计算在 MDCKII 细胞中进行的荧光累积研究中转运蛋白的 50％抑制常数 (IC_{50}) 值，其被定义为 50％抑制最大转运蛋白特异性转运所需的测试物品浓度。如先前所述计算来自 caco-2 或 MDCKII 细胞中的跨细胞实验的表观渗透率系数和外排比 (ER)（唐 (Tong) 等人 (2007) 抗微生物剂和化学疗法 (Antimicrob Agents Chemother)51：3498-504)。在适当时，测试条件之间观察到的统计差异显著性使用配对双尾史都登氏 t 检验 (paired two-tailed Student′ s t test) 评估。

[0366] 经转染的 MDCKII 细胞中 Pgp 和 BCRP 的抑制：通过分别在 MDCKII-MDR1 和 MDCKII-ABCG2 细胞中监测共孵育对荧光探针底物钙黄绿素 AM 和 Hoechst33342 的 Pgp 依赖性和 BCRP 依赖性累积的作用来研究可比西他相对于利托那韦和已知转运抑制剂环孢霉素 A(cyclosporin A，CSA) 和烟曲霉毒素 C(fumitremorgin C) 对 Pgp 和 BCRP 的抑制。可比西他分别以 36±10μM 和 59±28μM 的 IC_{50} 值抑制 Pgp 和 BCRP。利托那韦在以近似的溶解度极限孵育于分析缓冲液 (20μM) 中时展示 35％的 Pgp 抑制和 21％的 BCRP 抑制。较高浓度的可比西他因其在中性 pH 值下＞ 35 倍较高水溶性而在分析中是可实现的。浓度差异较大的可比西他和利托那韦可基于其在酸性条件下各别的溶解度存在于胃肠 (GI) 道中。合起来，溶解度和抑制结果指示可比西他相对于利托那韦在 GI 道中具有类似的 Pgp 和 BCRP 抑制。

[0367] 经转染的 MDCKII 细胞中的 Pgp 和 BCRP 底物分析：为了进一步表征可比西他与 Pgp（多药耐药蛋白 1；MDR1) 和 BCRP 的机械相互作用，在经人类转运蛋白的基因转染的细胞中完成双向渗透率分析以确定可比西他是否是这些外排转运蛋白的底物（图 10)。在 MDCKII-WT、MDCKII-MDR1（图 10A) 和 MDCKII-BCRP 细胞中评估可比西他 (10μM) 的双向渗透率（图 10B)。黑色条展示顶端到底外侧 (A-B) 渗透率，且空白条展示底外侧到顶端 (B-A) 渗透率。外排比指示在每一实验条件的图式上方。CSA(10μM) 和 Ko134(10μM) 分别用作 Pgp 和 BCRP 的已知抑制剂。结果是来自在存在或不存在各别抑制剂下比较野生型 MDCKII(MDCKII-WT) 与 MDCKII-MDR1 或 MDCKII-BCRP 细胞的代表性并行实验的一式二份孔的平均值。Pgp 或 BCRP 在 MDCKII 细胞中的过度表达增大可比西他的外排比。这些增大的外排比反映出可比西他的正向渗透率减小和反向渗透率增大。与 Pgp 依赖性和 BCRP 依赖性转运一致，可比西他外排在 Pgp 抑制剂 CSA 和 BCRP 抑制剂 Ko134 存在下减少。这些结果说明可比西他是 Pgp 和 BCRP 两者的底物，表明所观察到的抑制可能归因于对各别转运蛋白的结合位点的竞争。

[0368] 可比西他对模型 Pgp 和 BCRP 底物通过 caco-2 细胞单层的双向渗透率的作用：已报导 Caco-2 细胞为支持肠转运蛋白（包括 Pgp 和 BCRP) 的极化表达的 GI 吸收的生理上相关的模型系统。研究了可比西他 (COBI；90μM) 和利托那韦 (RTV；20μM) 对 10μM Pgp 底物地高辛（图 11A) 和 BCRP 底物哌唑嗪（图 11B) 通过 caco-2 细胞单层的双向渗透率的作用。基于 FDA 和国际转运蛋白协会 (International Transporter Consortium) 的推荐，分别挑选地高辛和哌唑嗪作为 Pgp 和 BCRP 的模型底物。将已知 Pgp 抑制剂 CSA(10μM) 和 BCRP 抑制剂烟曲霉毒素 C(2μM；在图 11B 中指示为“FTC”) 用作阳性对照。黑色条展示顶

端到底外侧 (A-B) 渗透率，且空白条展示底外侧到顶端 (B-A) 渗透率，且外排比指示在每一实验条件的图式上方。结果是一式两份进行的至少四次独立实验的平均值 ± 标准偏差，且统计显著性通过使用配对双尾史都登氏 t 检验与无共处理孔比较结果来评估 (*，P ＜ 0.05 ；**，P ＜ 0.01)。与已知 Pgp 抑制剂 CSA 类似，可比西他和利托那韦显著减小地高辛的外排比且显著增加顶端到底外侧 (A-B) 渗透率 (图 11A)。在研究可比西他和利托那韦相对于已知 BCRP 抑制剂烟曲霉毒素 C 对 BCRP 底物哌唑嗪的渗透率的作用的实验中观察到类似的作用 (图 11B)。这些数据表明可比西他和利托那韦对哌唑嗪的地高辛介导的和 BCRP 介导的转运的 Pgp 介导的转运的类似的抑制作用。

[0369] 可比西他对 HIV 蛋白酶抑制剂和 GS-7340 通过 caco-2 细胞单层的双向渗透率的作用 ：评估了可比西他 (90μM) 和利托那韦 (20μM) 对 HIV 蛋白酶抑制剂 (PI) 阿扎那韦、地瑞那韦、咯匹那韦和 GS-8374、实验 HIV PI 通过 caco-2 细胞单层的双向渗透率的作用。使用 10μM HIV PI 阿扎那韦 (图 12A)、地瑞那韦 (图 12B)、咯匹那韦 (图 12C) 和 GS-8374(图 12D) 评估 RTV 和 COBI 的作用。黑色条展示顶端到底外侧 (A-B) 渗透率，且空白条展示底外侧到顶端 (B-A) 渗透率，且外排比指示在每一实验条件的图式上方。结果是一式两份进行的至少四次独立实验的平均值 ± 标准偏差，且统计显著性通过使用配对双尾史都登氏 t 检验与无共处理孔比较定向结果来评估 (*，P ＜ 0.05 ；**，P ＜ 0.01 ；***，P ＜ 0.001)。评估 COBI(90μM) 对 GS-7340(10μM) 经 2 小时时程以 A-B(图 12E) 和 B-A(图 12F) 方向通过 caco-2 单层的双向渗透率的作用。空心符号描绘存在 COBI 且实心符号描绘不存在 COBI。结果是来自两次独立实验的一式两份测量的平均值 ± 标准偏差。与将这些化合物报导为 Pgp 底物的先前研究一致，针对蛋白酶抑制剂中的每一者观察到显著外排。可比西他和利托那韦的共投与通过增大蛋白酶抑制剂的 A-B 通量且减小 B-A 通量来可比较地减小外排比 (图 12A-D)。经 2 小时监测可比西他对 GS-7340 跨越 caco-2 单层的渗透率的作用，且可比西他增大 GS-7340 的 A-B 通量，同时伴随地减小 B-A 通量 (图 12E-F)。

[0370] 这些结果支持可比西他可能起到抑制 GS-7340 的 Pgp 介导的肠道分泌的作用的假设。

[0371] 生物学实例 2

[0372] 在人中进行药物动力学研究以测定在三种剂量水平下的 GS-7340 暴露。将合格的个体随机分组以接受 8mg GS-7340 剂量、25mg GS-7340 剂量、40mg GS-7340 剂量、300mg 替诺福韦 (作为 TDF) 或与 GS-7340 匹配的安慰剂持续 10 天。(注意 ：GS-7340 的剂量以 GS-7340 的游离碱质量形式给出，甚至在给予其它形式的 GS-7340 时。) 除非个体被随机分组以接受基于开放标签给出的替诺福韦，否则 GS-7340 以盲目方式投与。

[0373] 图 1 展示患者在研究第 1 天的替诺福韦血浆浓度。顶部线条 (无符号) 展示用 300mg 替诺福韦 (作为 TDF) 给药的患者的替诺福韦浓度。下方紧接着的线条 (尖头朝下的三角形) 展示用 40mg GS-7340 给药的患者的替诺福韦浓度。下方紧接着的线条 (尖头朝上的三角形) 展示用 25mg GS-7340 给药的患者的替诺福韦浓度。底部线条 (正方形) 展示用 8mgGS-7340 给药的患者的替诺福韦浓度。图式下方的表展示所获得的 Cmax 和 AUC 值。

[0374] 图 2 展示患者在研究第 10 天的替诺福韦血浆浓度。顶部线条 (菱形) 展示用 300mg 替诺福韦给药的患者的替诺福韦浓度。下方紧接着的线条 (尖头朝下的三角形) 展示用

40mg GS-7340 给药的患者的替诺福韦浓度。下方紧接着的线条（尖头朝上的三角形）展示用 25mg GS-7340 给药的患者的替诺福韦浓度。底部线条（正方形）展示用 8mg GS-7340 给药的患者的替诺福韦浓度。图式下方的表展示所获得的 Cmax 和 AUC 值。

[0375] 生物学实例 3

[0376] 在开放标记、交叉、单中心、多剂量、多群组研究中评估每日一次恩曲他滨 (FTC)/GS-7340 固定剂量组合、作为单一药剂的可比西他加强的地瑞那韦加 GS-7340 和依法韦仑或可比西他加强的地瑞那韦之间的药物相互作用可能性。

[0377] 表 4 展示研究的给药方案和时间表 .

[0378]

群组 1 (n = 12)		
群组	第 1-12 天	第 13-26 天
	疗法 A：在禁食条件下在早上每日一次投与 FTC/GS-7340 FDC (200/40 mg)	**疗法 B：**在禁食条件下在早上每日一次投与 FTC/GS-7340 FDC(200/40 mg) 加依法韦仑 (EFV)600 mg
群组 2 (n = 12)		
群组	第 1-12 天	第 13-22 天
	疗法 C：在进食条件下在早上每日一次投与 FTC/GS-7340 FDC (200/25 mg)	**疗法 D：**在进食条件下在早上每日一次投与 FTC/GS-7340 FDC(200/25 mg)加可比西他加强的地瑞那韦(DRV/co；800/150 mg)
群组 3 (n= 14)		
群组	第 1-10 天	第 11-22 天
	疗法 E：在进食条件下在早上每日一次投与可比西他加强的地瑞那韦 (DRV/co：800/150 mg)	**疗法 F：**在进食条件下在早上每日一次投与 FTC/GS-7340 FDC(200/25 mg)加可比西他加强的地瑞那韦(DRV/co：800/150 mg)
群组 4 (n = 12)；		
群组	第 1-12 天	第 13-22 天

[0379]

	疗法 G：在进食条件下在早上每日一次投与 GS-7340(8 mg)单一药剂	**疗法 H：**在进食条件下在早上每日一次投与 GS-7340(8 mg)单一药剂加可比西他(150 mg)

[0380] 表 4

[0381] 这一研究中的药物动力学分析结果展示在图 3-5 中。（注意 :GS-7340 的剂量以 GS-7340 的游离碱质量形式给出，甚至在给予其它形式的 GS-7340 时。）

[0382] 图 3A 展示在来自群组 1 的患者中针对恩曲他滨和 GS-7340（尖头朝上的三角形）以及恩曲他滨、GS-7340 和依法韦仑（（初始值＝ 100ng/ml）;尖头朝下的三角形）的剂量的 GS-7340（替诺福韦艾拉酚胺）浓度 (ng/ml)。GS-7340 暴露的 Cmax 和 AUC 结果展示在下表中。针对恩曲他滨和 GS-7340（上方线条 ;尖头朝上的三角形）以及恩曲他滨、GS-7340 和依法韦仑（下方线条 :尖头朝下的三角形）剂量的替诺福韦 (TFV) 浓度展示在图 3B 中。替诺福韦暴露的 Cmax 和 AUC 结果展示在下表中。

[0383] 图 4A 展示在来自群组 2 的患者中针对恩曲他滨和 GS-7340（尖头朝上的三角形）以及恩曲他滨、GS-7340、地瑞那韦和可比西他（尖头朝下的三角形）的剂量的 GS-7340 浓度 (ng/ml)。GS-7340 暴露的 C_{max} 和 AUC 结果展示在下表中。针对恩曲他滨和 GS-7340（尖

头朝上的三角形）以及恩曲他滨、GS-7340、地瑞那韦和可比西他（尖头朝下的三角形）剂量的替诺福韦（TFV）浓度展示在图 4B 中。替诺福韦暴露的 C_{max} 和 AUC 结果展示在下表中。

[0384] 图 5A 展示针对单独 GS-7340 以及 GS-7340 和可比西他（尖头朝上的三角形）剂量的 GS-7340 浓度（ng/ml）。GS-7340 暴露的 C_{max} 和 AUC 结果展示在下表中。针对单独 GS-7340（尖头朝上的三角形）以及 GS-7340 和可比西他（尖头朝下的三角形）剂量的替诺福韦（TFV）浓度展示在图 5B 中。替诺福韦暴露的 C_{max} 和 AUC 结果展示在下表中。

[0385] 在以 GS-7340(8mg) 加 COBI(150mg) 对作为单独药剂的 GS-7340(8mg) 形式给药时观察到 GS-7340（替诺福韦艾拉酚胺）和 TFV 的暴露增加。GS-7340$AUC_{最后}$和 C_{max} 分别约 2.7 和 2.8 倍更高，而 TFV AUC_{τ} 和 C_{max} 分别约 3.3 和 3.3 倍更高。这些数据表明所述相互作用是 COBI 介导的，很可能归因于替诺福韦艾拉酚胺 (GS-7340) 对 Pgp 介导的肠道分泌的抑制。

[0386] 生物学实例 4

[0387] GS-7340 和可比西他在临床试验中与埃替格韦和恩曲他滨一起投与以测定这些化合物的相对生物利用度。化合物相对于来自埃替格韦 / 可比西他 / 恩曲他滨 / 替诺福韦（参考）或 GS-7340(TFV)（参考）的暴露（埃替格韦、可比西他、恩曲他滨）使用 25mg 或 40mg 剂量的 GS-7340（测试）投与。具有类似设计的第二群组评估埃替格韦 / 可比西他 / 恩曲他滨 /GS-7340STR 的替代调配物。（注意：化合物的剂量以 GS-7340 的游离碱质量形式给出，甚至在给予其它形式的 GS-7340 时。）埃替格韦 / 可比西他 / 恩曲他滨 /GS-7340（单层）片剂通过将恩曲他滨 /GS-7340 制粒与埃替格韦制粒和可比西他掺合、片剂压缩、片剂膜包衣以及封装来制造。埃替格韦 / 可比西他 / 恩曲他滨 /GS-7340 双层片剂通过压缩埃替格韦 / 可比西他层和恩曲他滨 /GS-7340 层、片剂膜包衣以及封装来制造。为了提供测试对参考疗法之间的药物动力学比较的稳定评估，在每一群组中使用平衡威廉姆斯 4×4 设计 (balanced Williams4×4design)。

[0388] 埃替格韦 / 可比西他 / 恩曲他滨 /GS-7340 中的埃替格韦剂量 (150mg)、加强性可比西他剂量 (150mg) 和恩曲他滨剂量 (200mg) 代表在感染 HIV 的患者中证明持久功效和长期安全性的当前研究剂量（埃替格韦、可比西他）或市售剂量（恩曲他滨）。

[0389] 评估使用由二十名患者组成的两个群组。在群组 1 中，投与以下研究疗法。

[0390] 疗法 A：持续 12 天在上午每日一次投与 1× 单一片剂方案 (STR) 的调配物 1(150mg 埃替格韦加 150mg 可比西他加 200mg 恩曲他滨加 25mg GS-7340（呈 31.1mg 反丁烯二酸盐 GS-7340-02 形式））。

[0391] 疗法 B：持续 12 天在上午每日一次投与 1×STR 调配物 1(150mg 埃替格韦加 150mg 可比西他加 200mg 恩曲他滨加 40mg GS-7340（呈 49.7mg 反丁烯二酸盐 GS-7340-02 形式））。

[0392] 疗法 C：持续 12 天在上午每日一次投与 1×STR(150mg 埃替格韦加 150mg 可比西他加 200mg 恩曲他滨加 300mg 替诺福韦（呈反丁烯二酸替诺福韦酯形式））。

[0393] 疗法 D：持续 12 天在上午每日一次投与 1×25mg GS-7340 片剂。

[0394] 将患者随机分组到四种顺序 (I、II、III、IV) 中的一者中。

[0395]

	第 1-12 天	第 15-26 天	第 29-40 天	第 43-54 天
顺序 I	A	B	C	D
顺序 II	B	D	A	C
顺序 III	C	A	D	B
顺序 IV	D	C	B	A

[0396] 调配物 1(单层)通过将恩曲他滨 /GS-7340 制粒与埃替格韦制粒和可比西他掺合、片剂压缩、片剂膜包衣以及封装来制备。EVG/COBI/FTC/GS-7340STR 片剂核心含有胶体二氧化硅、交联羧甲基纤维素钠、羟基丙基纤维素、一水合乳糖、微晶纤维素、月桂基硫酸钠和硬脂酸镁作为非活性成分且经聚乙烯醇、聚乙二醇、滑石和二氧化钛膜包衣。

[0397] 在群组 2 中,投与以下研究疗法 :

[0398] 疗法 E :持续 12 天在上午每日一次投与 1×STR 调配物 2(150mg 埃替格韦加 150mg 可比西他加 200mg 恩曲他滨加 25mg GS-7340(呈 31.1mg 反丁烯二酸盐 GS-7340-02 形式))。

[0399] 疗法 F :持续 12 天在上午每日一次投与 1×STR 调配物 2(150mg 埃替格韦加 150mg 可比西他加 200mg 恩曲他滨加 40mg GS-7340(呈 49.7mg 反丁烯二酸盐 GS-7340-02 形式))。

[0400] 疗法 C :持续 12 天在上午每日一次投与 1×STR(150mg 埃替格韦加 150mg 可比西他加 200mg 恩曲他滨加 300mg 替诺福韦)。

[0401] 疗法 D :持续 12 天在上午每日一次投与 1×25mg GS-7340 片剂。

[0402] 将患者随机分组到四种顺序 (I、II、III、IV) 中的一者中。

[0403]

	第 1-12 天	第 15-26 天	第 29-40 天	第 43-54 天
顺序 I	E	F	C	D
顺序 II	F	D	E	C
顺序 III	C	E	D	F
顺序 IV	D	C	F	E

[0404] 调配物 2 被制备为通过压缩埃替格韦 / 可比西他层和恩曲他滨 /GS-7340 层、片剂膜包衣以及封装来制造的双层片剂。EVG/COBI/FTC/GS-7340STR 片剂核心含有胶体二氧化硅、交联羧甲基纤维素钠、羟基丙基纤维素、一水合乳糖、微晶纤维素、月桂基硫酸钠和硬脂酸镁作为非活性成分且经聚乙烯醇、聚乙二醇、滑石和二氧化钛膜包衣。

[0405] 图 6 展示来自在群组 1(调配物 1,单层)中治疗的患者的 GS-7340 的药物动力学数据。顶部线条(尖头朝下的三角形)展示在 40mg GS-7340 与可比西他一起投与时的 GS-7340 浓度 (ng/ml)。中部线条(尖头朝上的三角形)展示在 25mg GS-7340 与可比西他一起投与时的 GS-7340 浓度 (ng/ml)。底部线条(正方形)展示在 25mg GS-7340 单独投与时的 GS-7340 浓度 (ng/ml)。这些结果展示对于在 GS-7340 与可比西他一起投与时以 25mg 水平给药来说 2.2 倍更高的 GS-7340 水平。

[0406] 图 7 展示来自在群组 2(调配物 2,双层)中治疗的患者的 GS-7340 的药物动力学数据。顶部线条(尖头朝下的三角形)展示在 40mg GS-7340 与可比西他一起投与时的 GS-7340 浓度 (ng/ml)。中部线条(尖头朝上的三角形)展示在 25mg GS-7340 与可比西他一起投与时的 GS-7340 浓度 (ng/ml)。底部线条(正方形)展示在 25mg GS-7340 单独投与时的 GS-7340 浓度 (ng/ml)。这些结果也展示对于在 GS-7340 与可比西他一起投与时以 25mg 水平给药来说 2.2 倍更高的 GS-7340 水平。

[0407] 图 8 展示来自在群组 1(调配物 1,单层)中治疗的患者的替诺福韦的药物动力学数据。顶部线条(无符号)展示在 300mg 替诺福韦与可比西他一起投与时的替诺福韦浓度 (ng/ml)。下方紧接着的线条(尖头朝上的三角形)展示在 40mg GS-7340 与可比西他一起投与时的替诺福韦浓度 (ng/ml)。下方紧接着的线条(正方形)展示在 25mg GS-7340 与可比西他一起投与时的替诺福韦浓度 (ng/ml)。底部线条(尖头朝下的三角形)展示在 25mgGS-7340 单独投与时的替诺福韦浓度 (ng/ml)。这些结果也展示对于在替诺福韦或 GS-7340 与可比西他一起投与时以 25mg 水平给药来说 3-4 倍更高的替诺福韦水平。

[0408] 图 9 展示来自在群组 2(调配物 2,双层)中治疗的患者的替诺福韦的药物动力学数据。顶部线条(圆圈)展示在 300mg 替诺福韦与可比西他一起投与时的替诺福韦浓度 (ng/ml)。下方紧接着的线条(尖头朝上的三角形)展示在 40mg GS-7340 与可比西他一起投与时的替诺福韦浓度 (ng/ml)。下方紧接着的线条(正方形)展示在 25mg GS-7340 与可比西他一起投与时的替诺福韦浓度 (ng/ml)。底部线条(尖头朝下的三角形)展示在 25mg GS-7340 单独投与时的替诺福韦浓度 (ng/ml)。这些结果也展示对于在替诺福韦或 GS-7340 与可比西他一起投与时以 25mg 水平给药来说 3-4 倍更高的 GS-7340 水平。

[0409] 在投与 EVG/COBI/FTC/GS-7340(25mg) 调配物 1 和 2 之后,相对于作为单独药剂的 GS-7340(25mg),几何平均 GS-7340 和 TFV 暴露实质上更高。在 EVG/COBI/FTC/GS-7340(25mg) 的两种调配物情况下,GS-7340$AUC_{最后}$和 C_{max} 分别约 2.2 倍和 2.3 倍更高,而 TFV AUC_{τ} 和 C_{max} 分别约 3.1 倍和 3.7 倍更高。GS-7340 和 TFV 暴露在 EVG/COBI/FTC/GS-7340(40mg) 对 EVG/COBI/FTC/GS-7340(25mg) 之后通常呈剂量比例的。

[0410] 生物学实例 5

[0411] GS-7340 与埃替格韦 (EVG)、可比西他 (COBI) 和恩曲他滨 (FTC) 共调配到单一片剂方案 (STR) 中。在三名健康个体研究中,评估 GS-7340 和 COBI 之间的 EVG/COBI/FTC/GS-7340STR 的多剂量药物动力学 (PK) 和 / 或相互作用可能性,从而促进用于 STR 临床发展的 GS-7340 剂量选择。

[0412] 在研究 1(n = 20) 中,个体接受 EVG/COBI/FTC/GS-7340(150/150/200/40 或 150/150/200/25mg)、EVG/COBI/FTC/TDF(150/150/200/300mg) 或单独 GS-734025mg(SA),呈平衡威廉姆斯 4×4 设计形式的 12 天 / 疗法。在研究 2(n = 12) 中,个体依序接受 GS-7340(8mg)SA(参考)持续 12 天和 GS-7340 加 COBI(8/150mg)(测试)持续 10 天。在研究 3(n = 34) 中,在两个群组(各自 2×2 交叉设计)中,个体接受 EVG/COBI/FTC/GS-7340(150/150/200/10mg)(测试,两个群组)、EVG 加 COBI(150/150mg)(参考,群组 1) 以及 FTC 加 GS-7340(200/25mg)(参考,群组 2),每一疗法给药 12 天。GS-7340 和 TFV 的统计比较使用几何平均比率 (GMR) 进行,且 90% 置信区间 (CI) 为 70% -143%(研究 1 :测试 = EVG/COBI/FTC/GS-7340,参考 = GS-7340SA)。在整个给药和随访中进行安全性评估。

[0413] 所有疗法通常都被良好耐受。研究 1 带来 19/20 完成者,且一人因不良事件 (AE ;横纹肌瘤 (2 级)在接受 GS-7340SA 的同时)中止。所有个体都完成研究 2,而 34 名个体中的 33 名完成研究 3。在所述研究中未观察到 3 级或 4 级 AE。在研究 1 中,当作为 EVG/COBI/FTC/GS-7340 给药时,GS-7340(25mg) 和所得 TFV 暴露相对于 GS-7340SA 实质上更高 (GMR(90% CI)GS-7340$AUC_{最后}$:222(200,246) 和 C_{max} :223(187,265) ;TFVAUC_{τ} :307(290,324),C_{max} :368(320,423))。在研究 2 中,当作为 GS-7340 加 COBI 相对于 GS-7340SA 给药

时，GS-7340 暴露类似地较高，表明在研究 1 中观察到的相互作用是 COBI 介导的 (GMR(90％ CI)GS-7340AUC $_{最后}$:265(229,307) 和 C_{max}:283(220,365)，TFVAUC$_{\tau}$:331(310,353)，C_{max}:334(302,370)，和 C_{τ}:335(312,359))。在研究 3 中，当 GS-7340 的剂量调整到 10mg 时，EVG/COBI/FTC/GS-7340(150/150/200/10mg) 对参考引起可比较的 GS-7340 和 TFV 暴露。(GMR(90 ％ CI)GS-7340AUC $_{最后}$:89.0(76.7,103) 和 C_{max}:97.3(82.1,115)，TFV AUC $_{最后}$:124(113,136)，C_{max}:113(98.8,129) 和 C_{τ}:120(103,140))。EVG/COBI/FTC/GS-7340STR 相对于参考疗法和历史数据提供类似的 EVG、COBI 和 FTC 暴露。

[0414] GS-7340 和 TFV 暴露在与 COBI 共投与或作为 EVG/COBI/FTC/GS-7340 给药之后增大约 2-3 倍，这可能归因于 GS-7340 对 Pgp 介导的肠道分泌的 COBI 抑制。在 10mg 剂量的 GS-7340 情况下，EVG/COBI/FTC/GS-7340 提供与 25mg GS-7340 可比较的 GS-7340 和 TFV 暴露和相对于 EVG/COBI/FTC/TDF 约 90％更低的 TFV 暴露。

[0415] 生物学实例 6

[0416] EVG/COBI/FTC/TDF 和 EVG/COBI/FTC/ 替诺福韦艾拉酚胺半反丁烯二酸盐以单一片剂方案 (STR) 形式在 2 期临床试验中投与，在未经 HIV+ 疗法治疗的成人中评估安全性和功效。所有个体均具有 HIV-1RNA ＞ 5000c/ml。第 24 周数据指示具有两个 STR 的疗法引起服用 EVG/COBI/FTC/ 替诺福韦艾拉酚胺半反丁烯二酸盐的 87％个体和服用 EVG/COBI/FTC/TDF 的 90％个体具有 HIV-1RNA ＜ 50c/ml。EVG/COBI/FTC/ 替诺福韦艾拉酚胺半反丁烯二酸盐被良好耐受，且相对于 EVG/COBI/FTC/TDF 的已知安全性特征，未鉴别出新的或出乎意外的不良药物反应。

[0417] 在第 24 周评估个体的肾功能。当与服用 EVG/COBI/FTC/TDF 的个体相比时，服用 EVG/COBI/FTC/ 替诺福韦艾拉酚胺半反丁烯二酸盐的个体的估计的肾小球滤过率 (eGFR) 显著减少更少、蛋白尿倾向于更少且肾小管性蛋白尿统计学上更少。这些差异可代表亚临床替诺福韦相关的肾中毒减少。

[0418] 为了评估骨矿物质密度，双能 X 射线吸收测量学扫描在基线和第 24 周进行。与服用 EVG/COBI/FTC/TDF 的个体相比，服用 EVG/COBI/FTC/ 替诺福韦艾拉酚胺半反丁烯二酸盐的个体在 24 周之后在脊柱和臀部两处的骨矿物质密度显著减少更小。重要的是，与 EVG/COBI/FTC/TDF 组相比，在 EVG/COBI/FTC/ 替诺福韦艾拉酚胺半反丁烯二酸盐组中髋骨矿物质密度从基线＞ 3％减少的个体的比例 10 倍更低 (3.0％对 31.6％)。

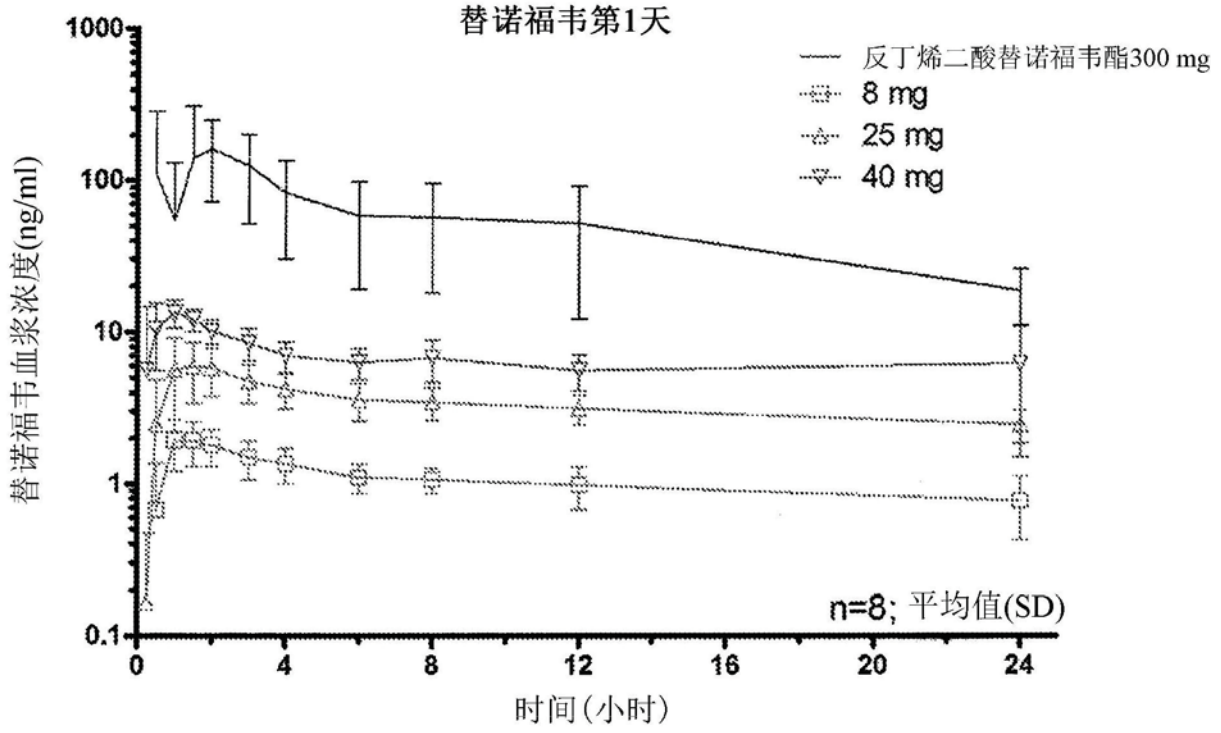
[0419] 合起来，这些数据支持以下假设 :TDF 相关的肾和骨毒性由循环替诺福韦驱动，因为投与 EVG/COBI/FTC/ 替诺福韦艾拉酚胺半反丁烯二酸盐的个体的替诺福韦水平减少 90％。

[0420] 所有本文中引用的参考文献、公开案、专利和专利文件均以引用的方式并入本文中，如同个别地以引用的方式并入一般。已经参考各种特定和优选实施例和技术来描述本发明。然而，应了解在保持在本发明的精神和范围内的同时，可以进行许多变化和修改。

[0421] 除非本文另外指出或明显与内容相矛盾，否则在描述本发明 (包括以下权利要求书) 的内容中使用术语“一 (a、an)”、“所述”和类似冠词等应理解为涵盖单数与复数两者。除非另外指出，否则术语“包含”、“具有”、“包括”和“含有”应理解为开放式术语 (即，意指“包括 (但不限于)”)。除非本文另外指示，否则本文中值范围的叙述仅打算充当个别提及属于所述范围的各独立值的速记方法，且各独立值并入本说明书中，如同在本文中个别地

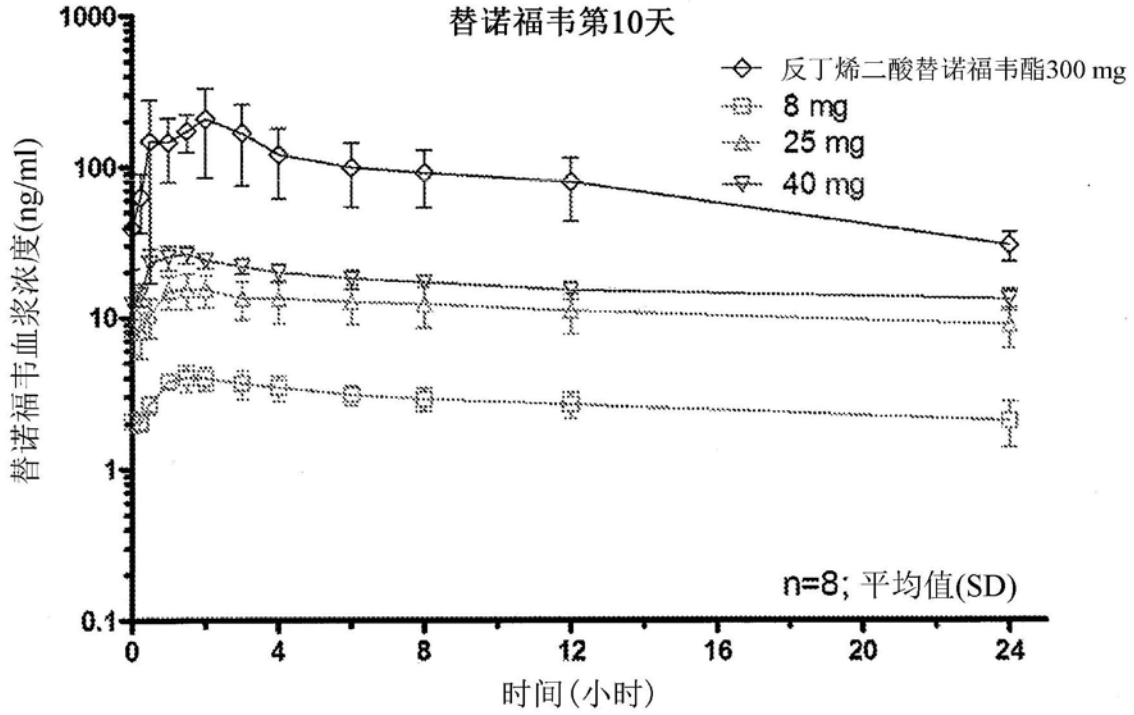
叙述一般。除非本文另外指出或另外明显与内容相矛盾，否则本文所述的所有方法可以任何合适顺序进行。除非另外要求，否则使用任何和所有实例或本文提供的示例性语言（例如，“如”）仅打算更好地阐明本发明且并不对本发明的范围施加限制。本说明书中的任何语言均不应理解为指示实施本发明所必需的任何未要求要素。

[0422] 本说明书内的实施例提供本发明的实施例的说明且不应被理解为限制本发明的范围。熟练技术人员认识到所要求的本发明涵盖其它实施例，且本说明书和实例打算被视为仅具示例性，且本发明的真实范围和精神由所附权利要求书指定。



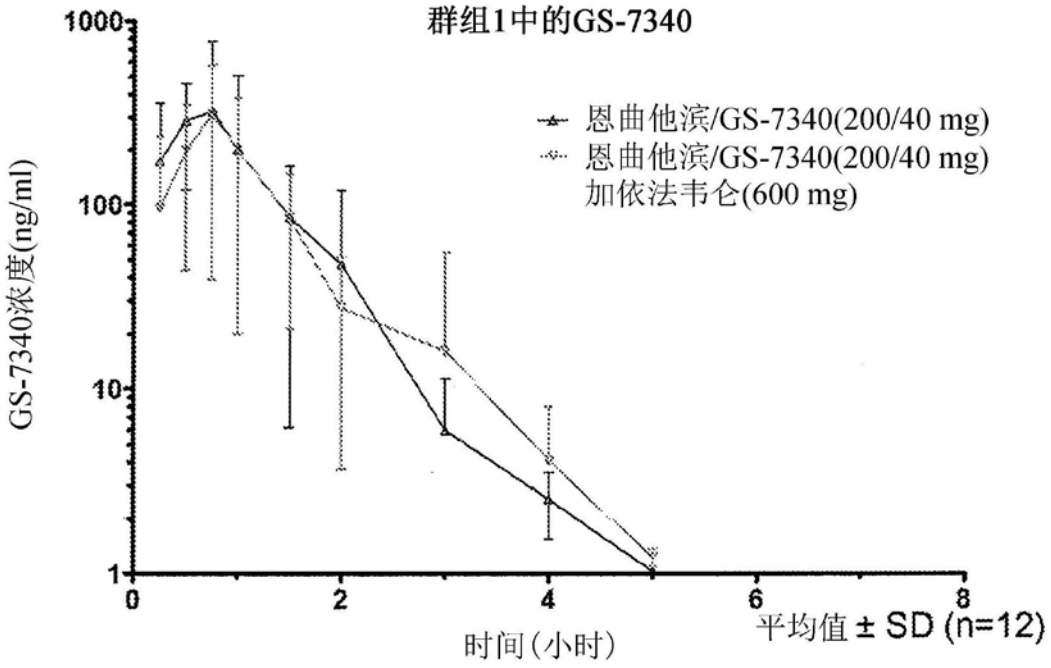
第1天药物动力学 平均值(CV%)	GS-7340 8 mg	GS-7340 25 mg	GS-7340 40 mg	反丁烯二酸替诺福韦酯 300 mg
Cmax (ng/ml)	2 (30)	6.5 (40)	15 (36)	210 (52)
AUC最后(ng.hr/ml)	25 (27)	70 (37)	143 (40)	1132 (48)

图 1



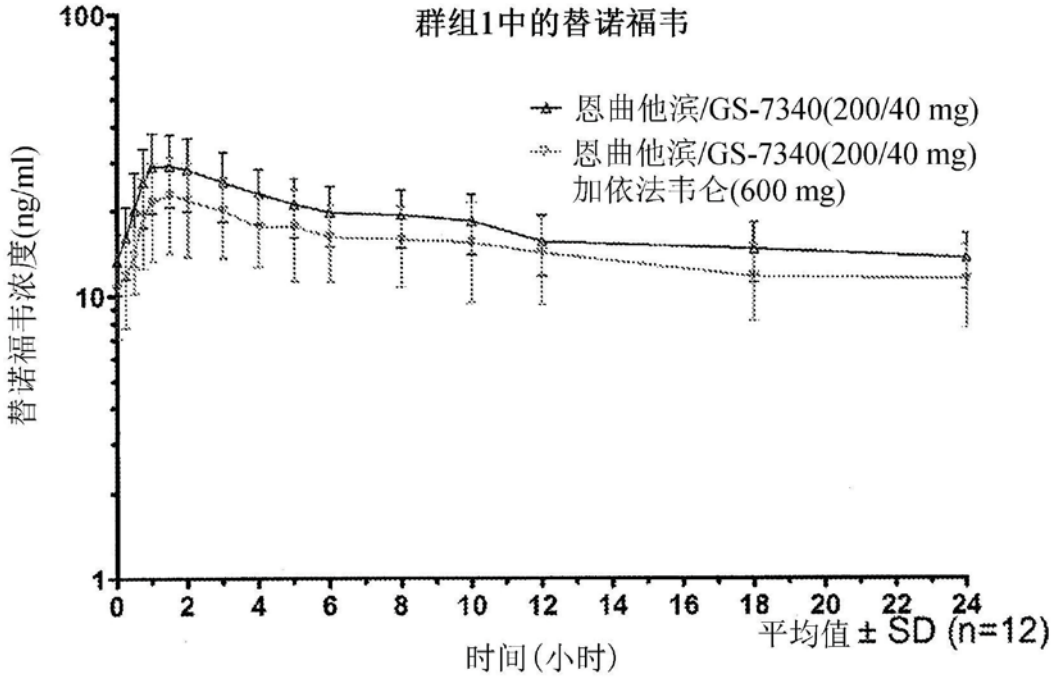
第10天药物动力学 平均值(CV%)	GS-7340 8 mg	GS-7340 25 mg	GS-7340 40 mg	反丁烯二酸 替诺福韦酯 300 mg
Cmax (ng/ml)	3.9 (28)	16 (22)	28 (9)	260 (43)
AUCτ (ng.hr/ml)	66 (19)	268 (29)	389 (11)	2090 (44)

图 2



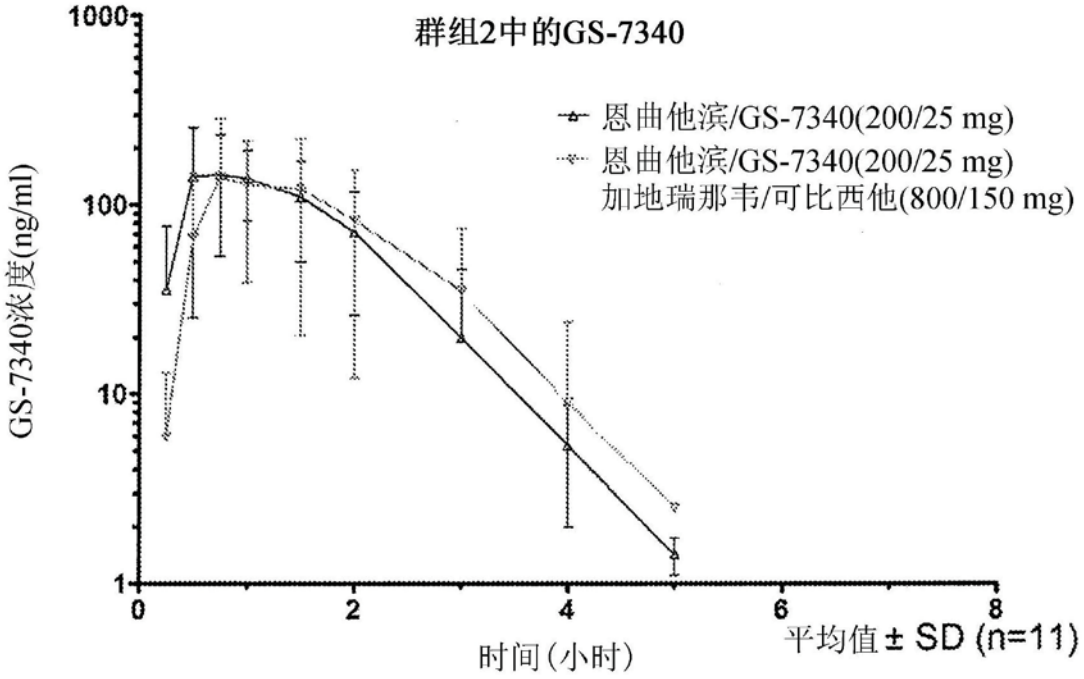
	群组1中的GS-7340药物动力学	
平均值(CV%)	恩曲他滨/GS-7340 (200/40 mg)	恩曲他滨/GS-7340 加依法韦仑600 mg
$AUC_{最后}$ (ng.hr/ml)	330.5 (63)	285.5 (47)
C_{max} (ng/ml)	481.3 (83)	390.8 (62)

图 3A



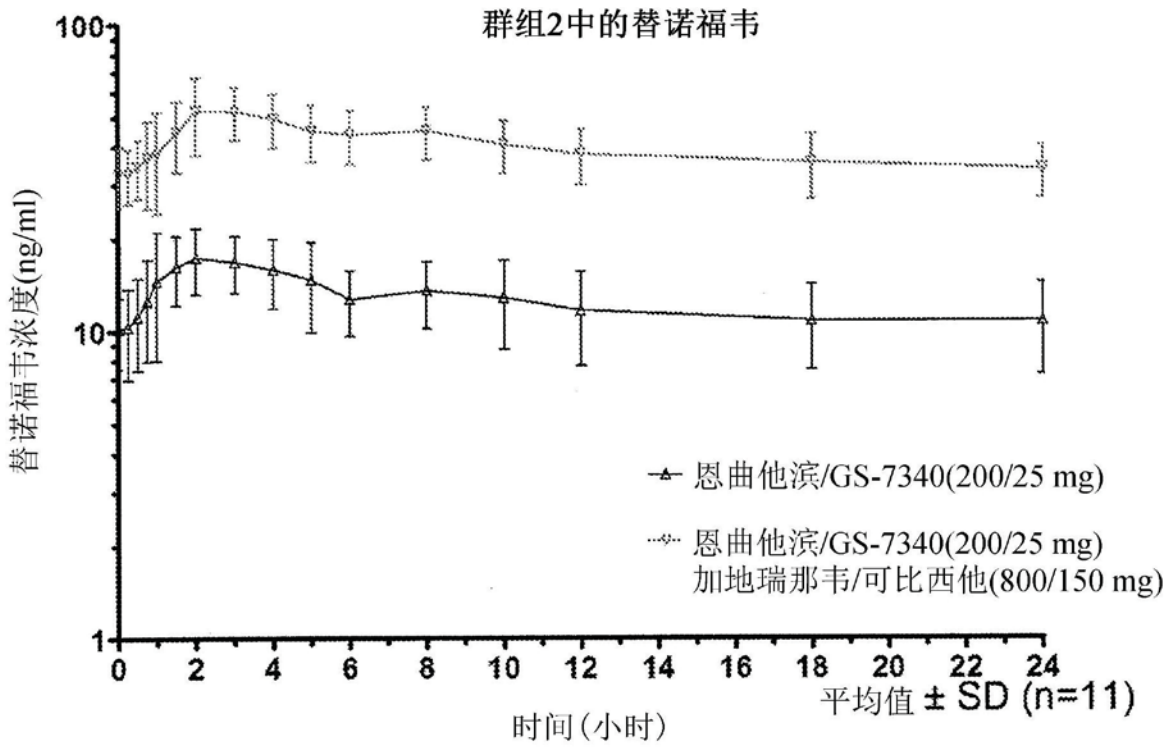
	群组1中的替诺福韦药物动力学	
平均值(CV%)	恩曲他滨/GS-7340 (200/40 mg)	恩曲他滨/GS-7340 加依法韦仑600 mg
AUC_{0-24} (ng.hr/ml)	427.5 (23)	350.2 (32)
C_{max} (ng/ml)	31.4 (25)	24.0 (35)
C_{τ}(ng/ml)	13.5 (22)	11.3 (32)

图 3B



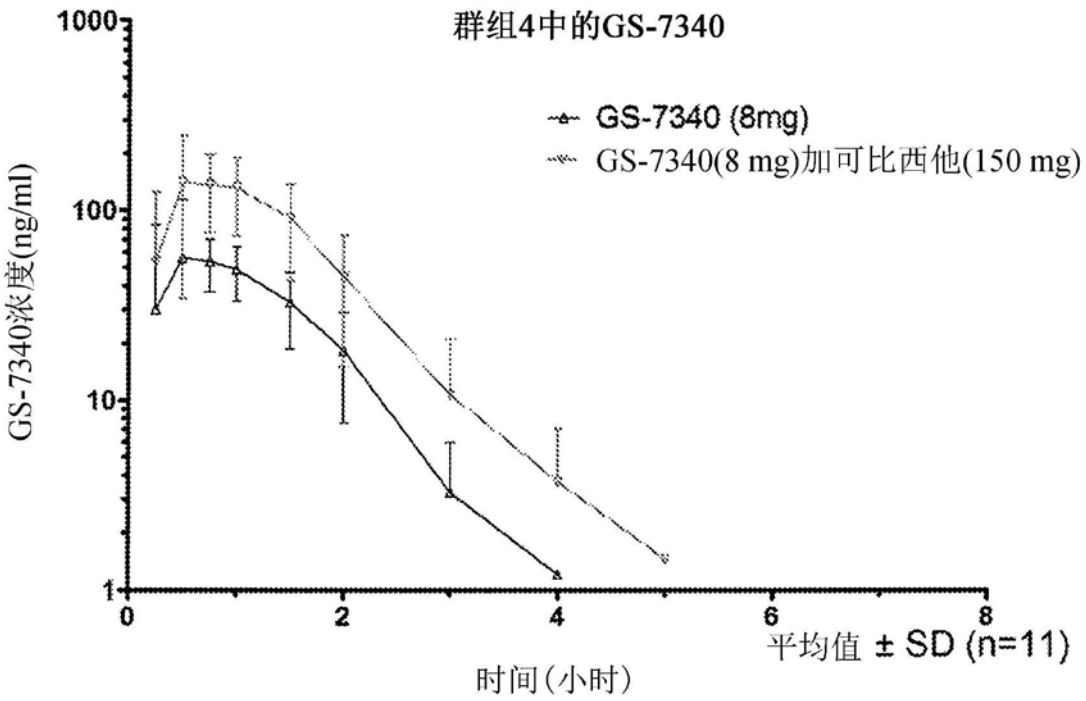
GS-7340药物动力学	群组2		群组3
平均值 (CV%)	恩曲他滨/ GS-7340 (200/25 mg)	恩曲他滨/ GS-7340加地瑞那韦/可比西他 (800/150 mg)	恩曲他滨/GS-7340(200/25 mg) 加地瑞那韦/可比西他(800/150 mg)
$AUC_{最后}$ (ng.hr/ml)	245.6 (42)	243.9 (41)	271.0 (39)
C_{max} (ng/ml)	208.3 (40)	215.0 (59)	287.4 (73)

图 4A



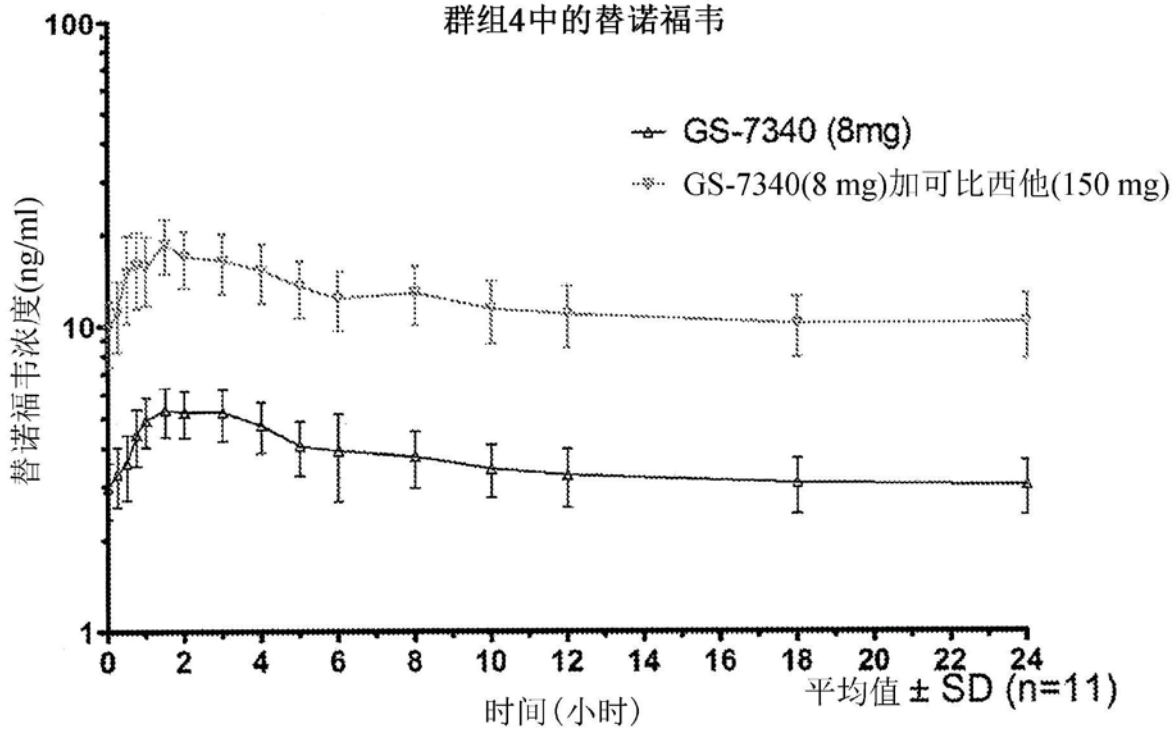
替诺福韦药物动力学	群组2		群组3
平均值 (CV%)	恩曲他滨/ GS-7340 (200/25 mg)	恩曲他滨/GS-7340 加地瑞那韦/可比西他(800/150 mg)	恩曲他滨/GS-7340(200/25 mg) 加地瑞那韦/可比西他(800/150 mg)
AUC_{τ} (ng.hr/ml)	299.2 (29)	953.4 (20)	967.6 (13)
C_{max} (ng/ml)	18.3 (28)	57.4 (23.2)	57.7 (15)
C_{τ} (ng/ml)	10.8 (33)	33.7 (20)	36.2 (13)

图 4B



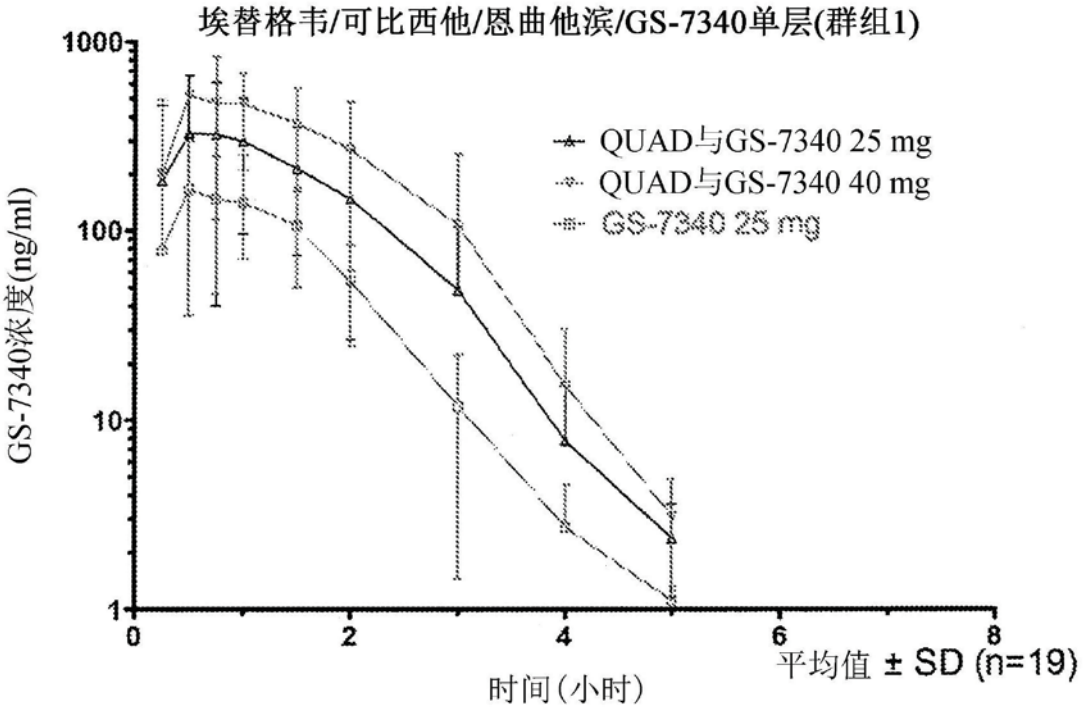
	群组4			
	稳态药物动力学		单剂量药物动力学	
平均值(CV%)	GS-7340 (8 mg)	GS-7340(8 mg) 加可比西他 (150 mg)	GS-7340 (8 mg)	GS-7340(8 mg) 加可比西他 (150 mg)
$AUC_{最后}$ (ng.hr/ml)	81.2 (44)	213.3 (38)	64.7 (34)	188.0 (27)
C_{max} (ng/ml)	71.0 (73)	189.9 (46)	49.9 (38)	141.5 (33)

图 5A



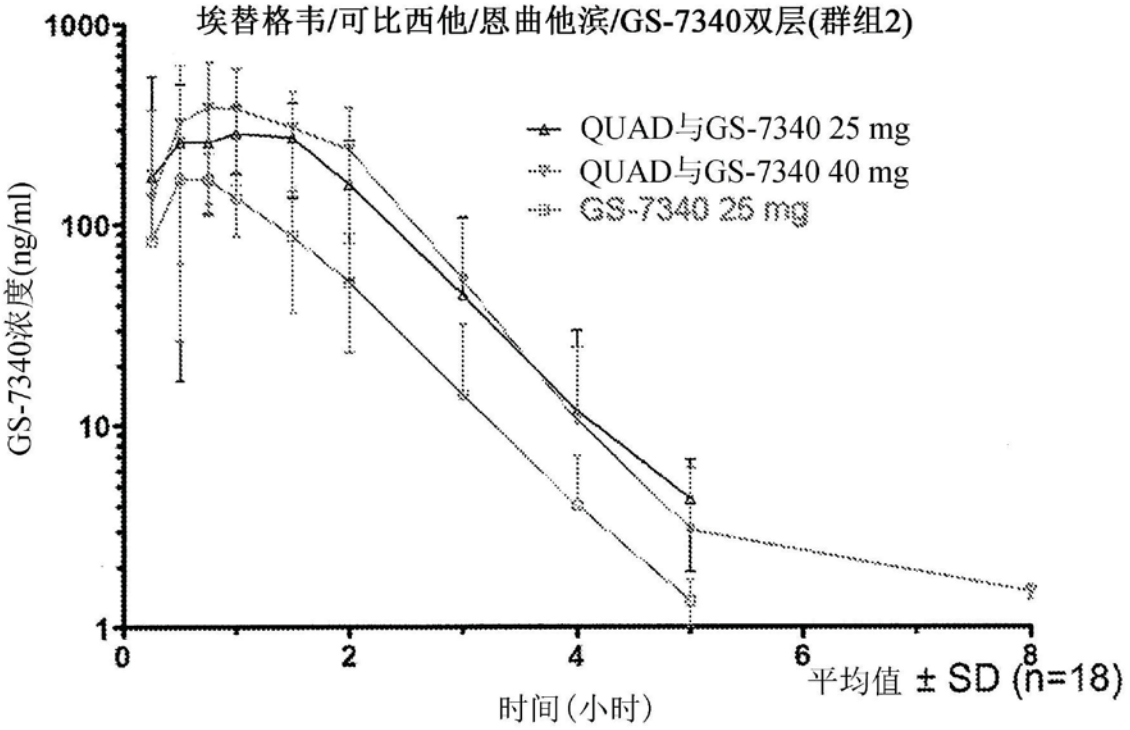
	替诺福韦药物动力学 多剂量药物动力学	
平均值(CV%)	GS-7340 (8 mg)	GS-7340(8 mg) 加可比西他(150 mg)
AUC_{τ} (ng.hr/ml)	86.1 (19)	286.9 (22)
C_{max} (ng/ml)	5.8 (19)	19.3 (20)
C_{τ} (ng/ml)	3.0 (20)	10.2 (24)

图 5B



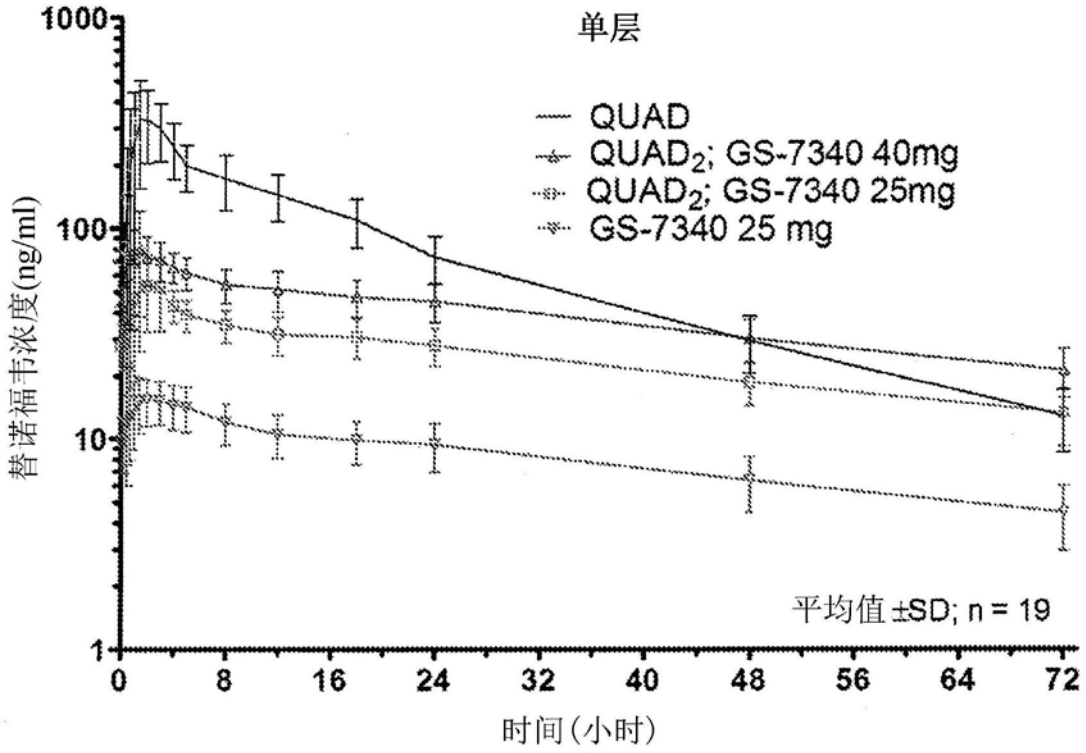
单层 平均值(CV%)	$QUAD_2$与 GS-7340 25 mg	$QUAD_2$与 GS-7340 40 mg	GS-7340 25 mg
C_{max} (ng/ml)	506 (54)	793 (52)	215 (55)
AUC_{τ} (ng.hr/ml)	552 (41)	929 (34)	243 (42)

图 6



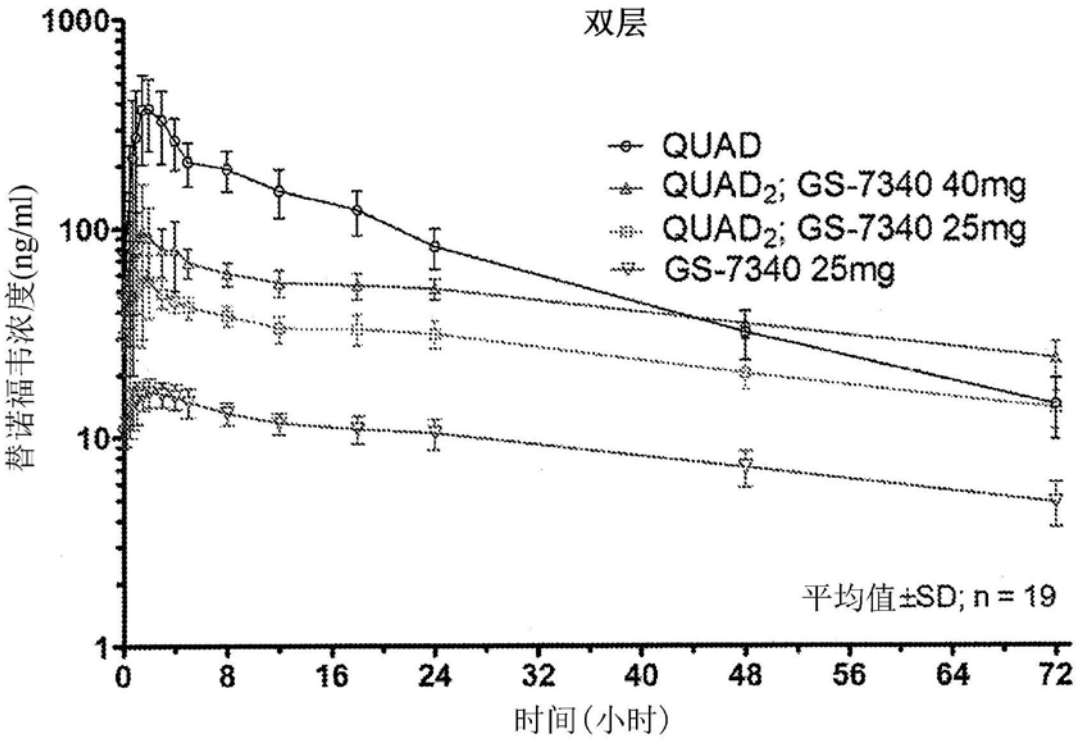
双层 平均值(CV%)	$QUAD_2$与 GS-7340 25 mg	$QUAD_2$与 GS-7340 40 mg	GS-7340 25 mg
C_{max} (ng/ml)	472 (58)	587 (33)	211 (44)
AUC_τ (ng.hr/ml)	559 (29)	760 (27)	245 (34)

图 7



单层 平均值(CV%)	$QUAD_2$ 25mg	$QUAD_2$ 40mg	GS-7340 25 mg	QUAD
C_{max} (ng/ml)	66 (51)	103 (64)	16 (25)	445 (29)
C_τ (ng/ml)	28.1 (20)	45.4 (21)	9.40 (26)	73.1 (25)
AUC_τ (ng.hr/ml)	837 (18)	1310 (21)	274 (24)	3760 (22)

图 8



双层 平均值(CV%)	$QUAD_2$ 25 mg	$QUAD_2$ 40 mg	GS-7340 25 mg	QUAD
C_{max} (ng/ml)	71.9 (57)	117 (60)	17.5 (15)	505 (27)
C_τ (ng/ml)	31.3 (15)	51.4 (12)	10.5 (17)	81.6 (22)
AUC_τ (ng.hr/ml)	899 (13)	1460 (16)	301 (13)	4120 (22)

图 9

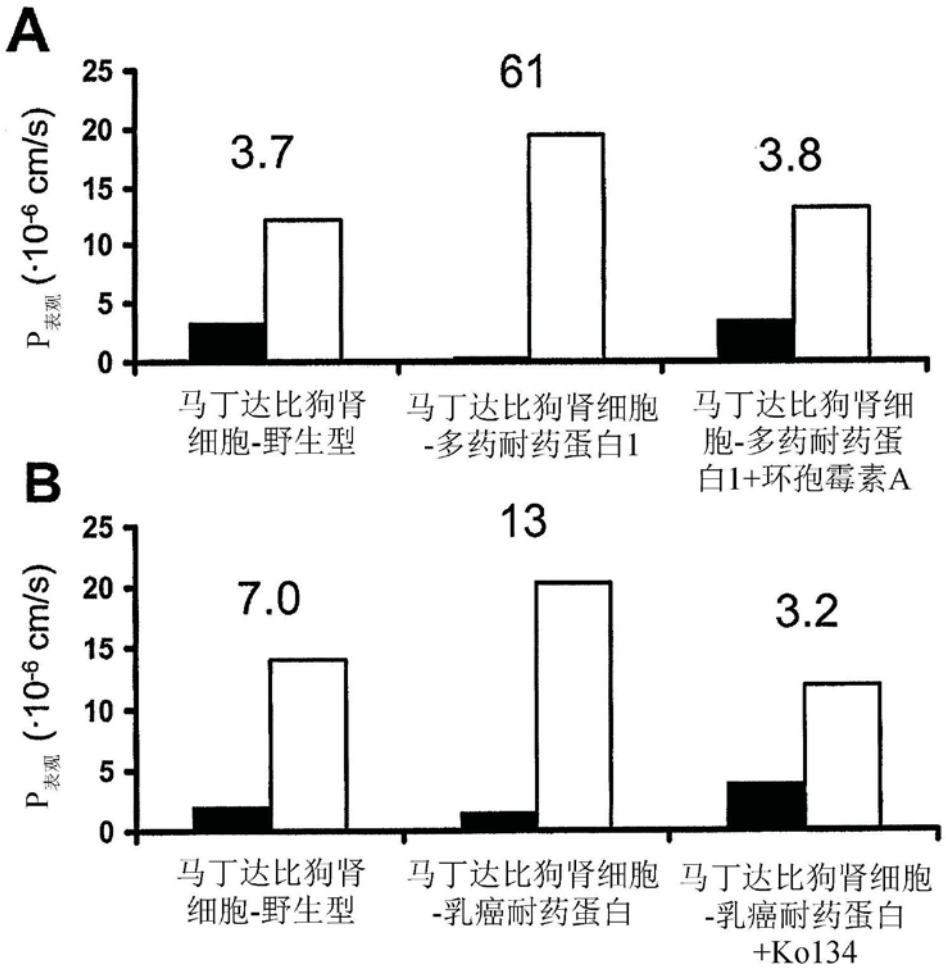

A
25
20
15
10
5
0
P表观 (·10-6 cm/s)
3.7
61
3.8
马丁达比狗肾细胞-野生型
马丁达比狗肾细胞-多药耐药蛋白1
马丁达比狗肾细胞-多药耐药蛋白1+环孢霉素A
B
25
20
15
10
5
0
P表观 (·10-6 cm/s)
7.0
13
3.2
马丁达比狗肾细胞-野生型
马丁达比狗肾细胞-乳癌耐药蛋白
马丁达比狗肾细胞-乳癌耐药蛋白+Ko134

图 10

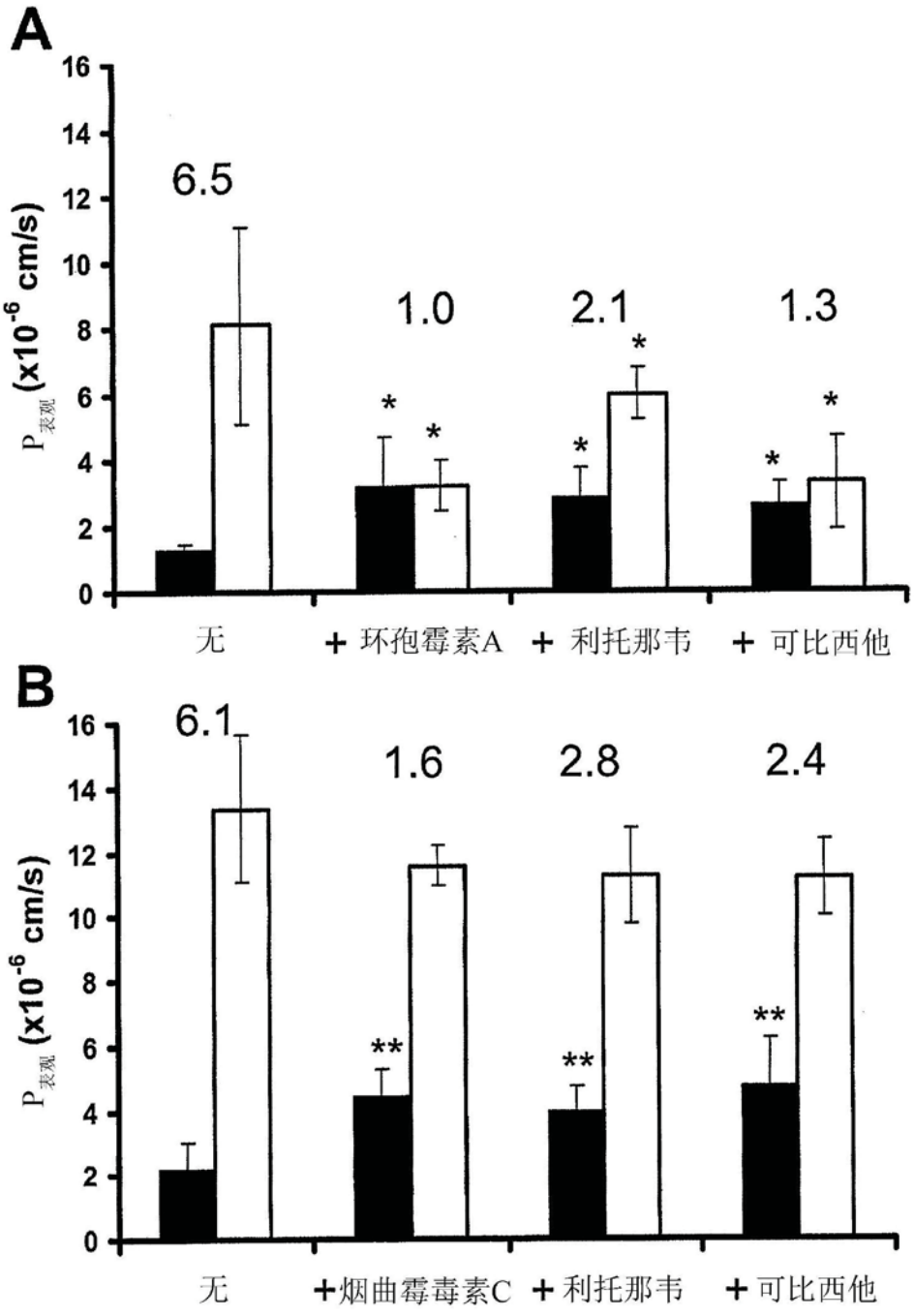

A
16
14
12
10
8
6
4
2
0
$P_{表观}$ ($x10^{-6}$ cm/s)
6.5
1.0
2.1
1.3
*
*
*
*
*
*
无
+ 环孢霉素A
+ 利托那韦
+ 可比西他
B
16
14
12
10
8
6
4
2
0
$P_{表观}$ ($x10^{-6}$ cm/s)
6.1
1.6
2.8
2.4
**
**
**
无
+烟曲霉毒素C
+ 利托那韦
+ 可比西他

图 11

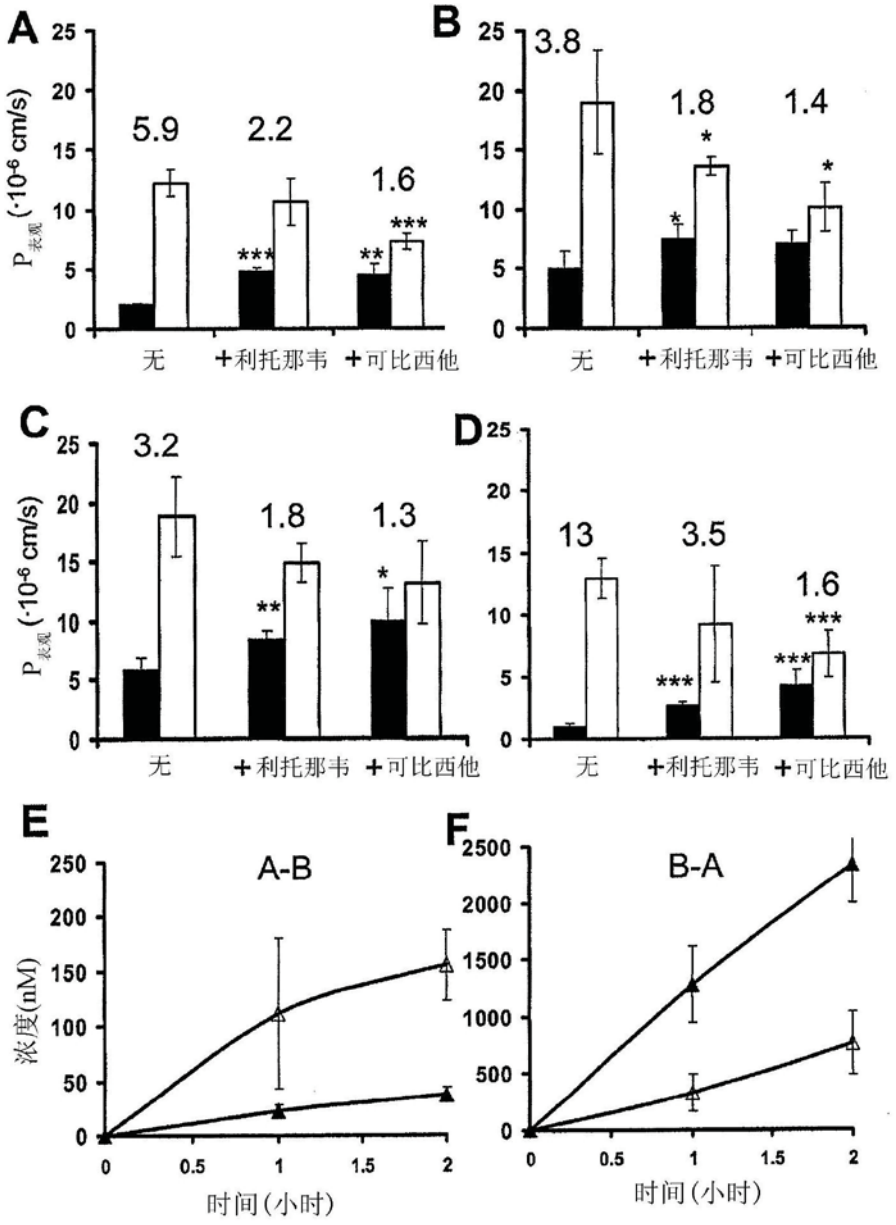

A
B
C
D
E
F
5.9
2.2
1.6
3.8
1.8
1.4
3.2
1.8
1.3
13
3.5
1.6
无
+利托那韦
+可比西他
A-B
B-A
浓度(nM)
时间(小时)

图 12

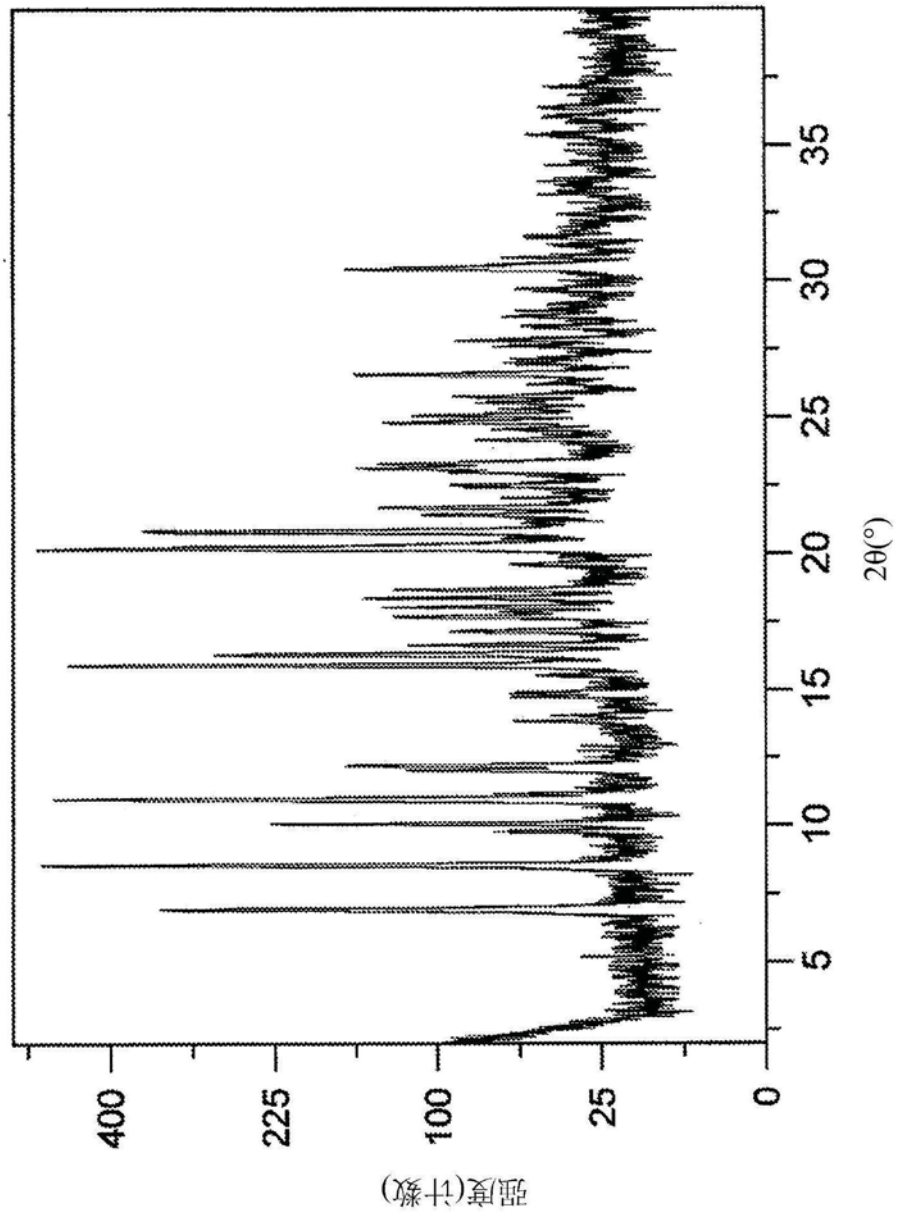


图 13

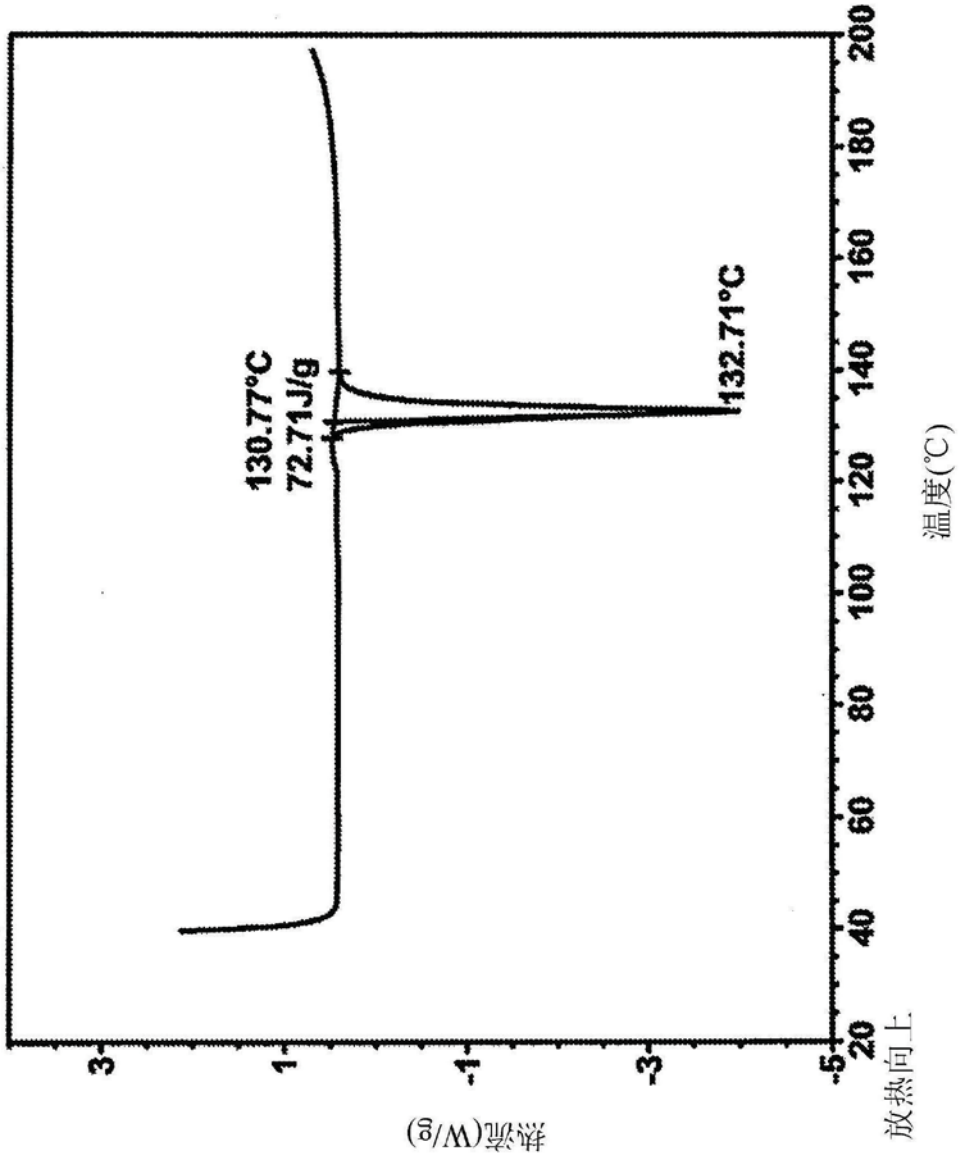

130.77°C
72.71J/g
132.71°C
热流(W/g)
放热向上
温度(°C)
3
1
-1
-3
-5
20
40
60
80
100
120
140
160
180
200

图 14

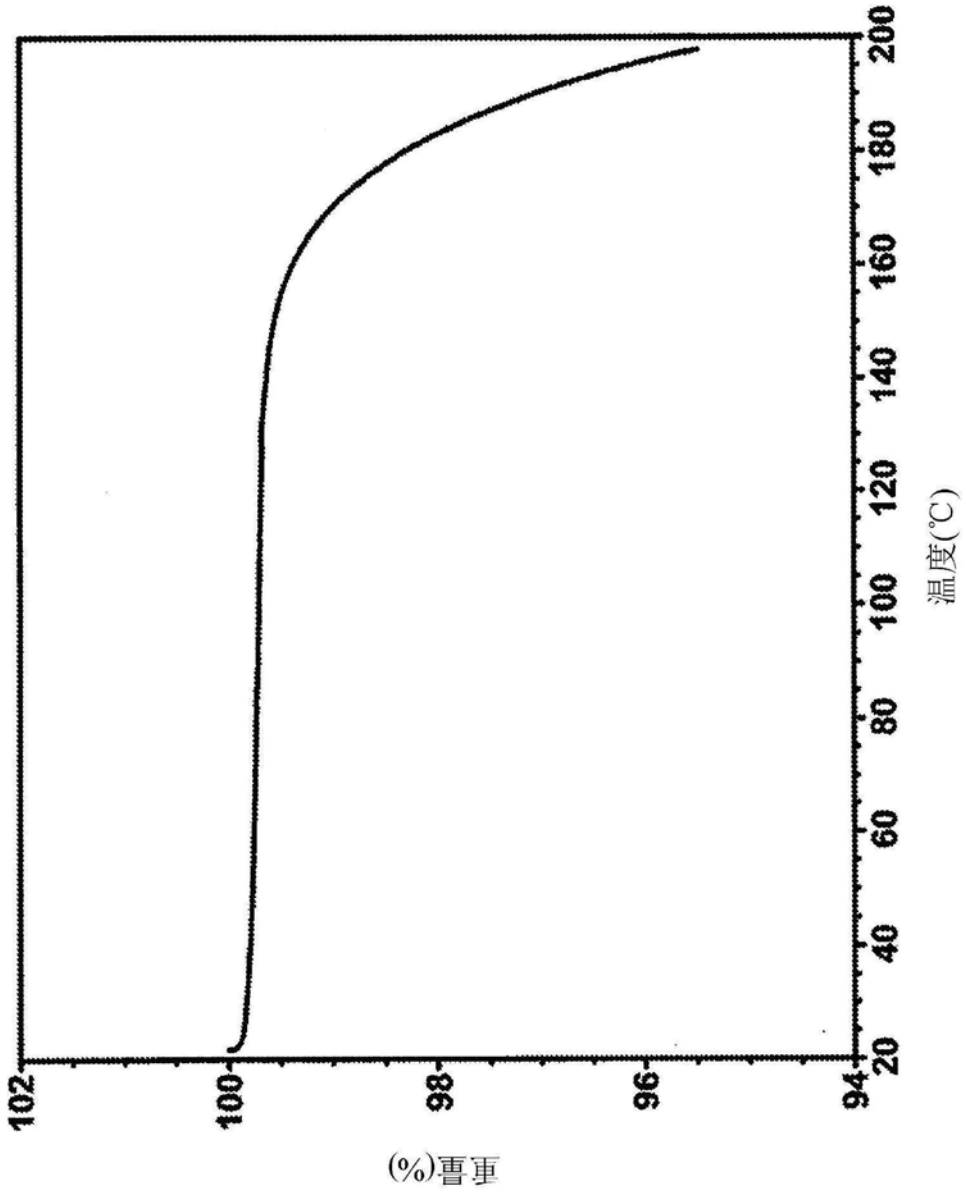


图 15

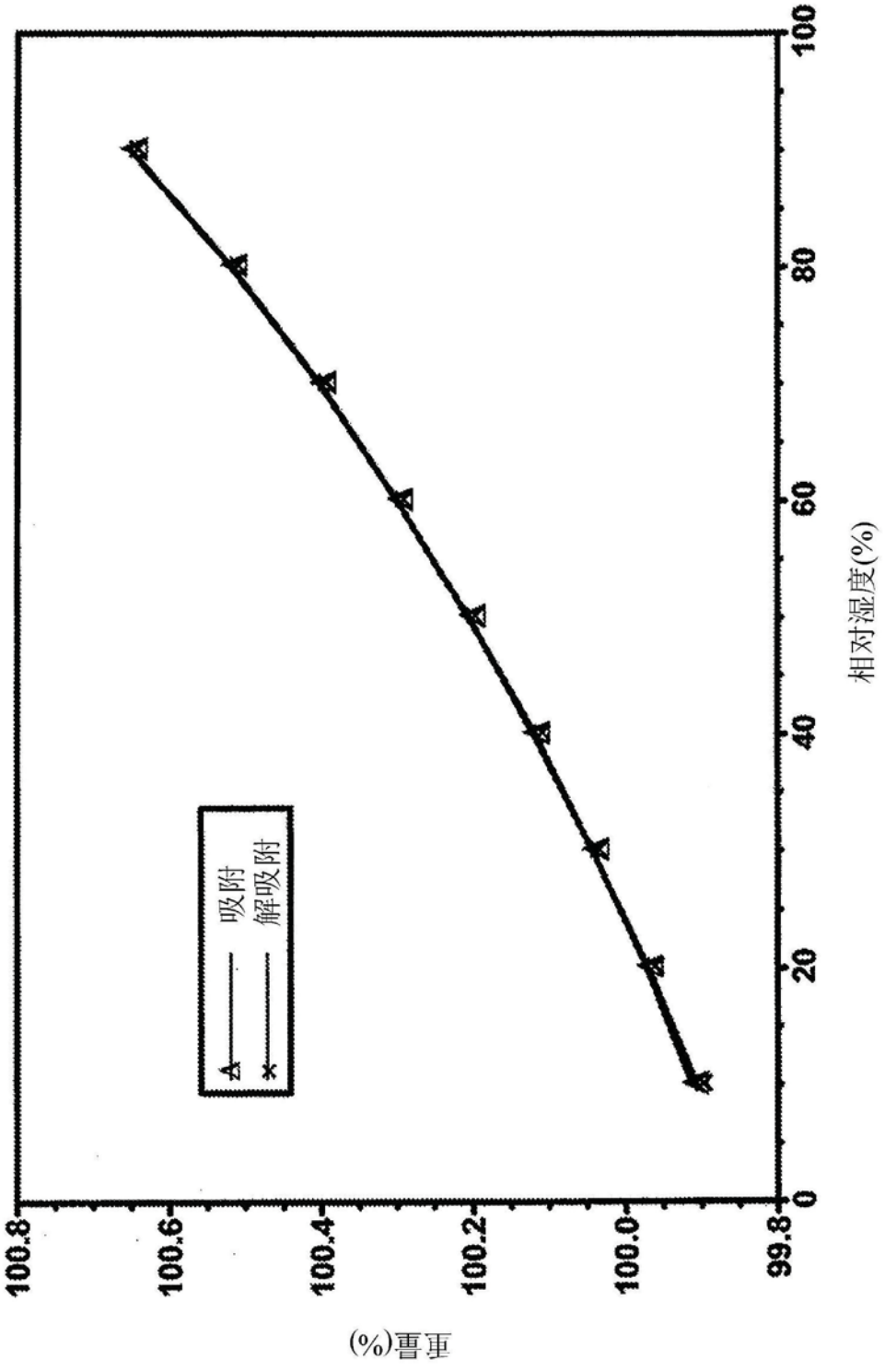


图 16