



(51) International Patent Classification:

A61K 31/497 (2006.01) *A61K 31/12* (2006.01)
A61K 31/7056 (2006.01) *A61K 31/18* (2006.01)
A61K 38/21 (2006.01)

(21) International Application Number:

PCT/US2012/024850

(22) International Filing Date:

13 February 2012 (13.02.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/441,920 11 February 2011 (11.02.2011) US
61/555,895 4 November 2011 (04.11.2011) US

(71) Applicant (for all designated States except US): **VERTEX PHARMACEUTICALS INCORPORATED** [US/US];
130 Waverly Street, Cambridge, Massachusetts 02139 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GARG, Varun** [US/US]; 23 LedgeWood Road, Framingham, Massachusetts 01701 (US).

(74) Agent: **O'BRIEN, Jonathan P.**; Honigman Miller Schwartz and Cohn LLP, 350 East Michigan Avenue, Suite 300, Kalamazoo, Michigan 49007 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: TREATMENT OF HCV IN HIV INFECTION PATIENTS

(57) Abstract: The disclosure relates to method of treatment, dosage regimens, and medicaments comprising telaprevir for the treatment of hepatitis C virus in a patient infected with HIV. Also disclosed are methods of treatment, dosage regimens, and medicaments comprising telaprevir in combination with one or more of an interferon, ribavirin or anti-HIV agent.



TREATMENT OF HCV IN HIV INFECTION PATIENTS**CROSS-REFERENCE**

- [0001] The present application claims priority to U.S. Application No. 61/441,920, filed on February 11, 2011 and U.S. Application No. 61/555,895, filed on November 4, 2011, the contents of which are incorporated herein by reference in their entireties.

TECHNICAL FIELD

- [0002] In general, the invention relates to therapies for the treatment of hepatitis C virus (HCV) in patients co-infected with HCV and human immunodeficiency virus (HIV) by administering telaprevir alone, or in combination with an interferon, ribavirin, an anti-HIV agent or any combination thereof.

BACKGROUND

- [0003] HCV co-infection is a major contributor to morbidity and mortality among patients with HIV infections. It has been reported that the prevalence of the HCV may be as high as 30 percent among patients infected with HIV and as high as 90 percent among patients who contracted HIV infection through injection drug use. Current United States Federal guidelines recommend that all HIV positive individuals be tested for HCV.
- [0004] A greater proportion of HIV/HCV co-infected patients may progress to cirrhosis (serious liver scarring), and liver disease progression is more rapid among those who are co-infected than among those with HCV alone. End-stage liver disease associated with HCV is now a major cause of death among patients infected with HIV. This accelerated rate is magnified in patients with low CD4 counts.
- [0005] HIV infection appears to adversely affect all stages of HCV infection, leading to increased viral persistence and accelerated progression of HCV-related liver disease. In turn, HCV infection also complicates HIV treatment due to the increased frequency of antiretroviral (ARV)-associated hepatotoxicity. Drug-induced liver injury (DILI) following anti-retroviral therapy (ART) is more common in HIV/HCV co-infected patients. The greatest risk of DILI may be observed in co-infected persons with advanced liver disease e.g., cirrhosis or end-stage liver disease. Eradication of HCV infection may decrease the likelihood of ARV-associated DILI.

[0006] Co-infection with HIV and HCV is a significant health care problem. Currently therapy with Pegasys (peginterferon alfa-2a) and Copegus (ribavirin) is the only U.S. Food and Drug Administration (FDA) approved medication to treat hepatitis C in people co-infected with HIV and hepatitis C. A significant proportion of treated co-infected patients do not achieve a sustained virologic response. Thus, there is a need for additional therapies which can effectively treat HIV patients at risk for HCV or co-infected with HCV.

SUMMARY

[0007] The current disclosure relates to the finding that the addition of telaprevir, an oral inhibitor of HCV protease, to the current regimen of Peg-IFN and RBV led to improved HCV viral responses in patients with HIV infection. Telaprevir is described in PCT Publication Number WO 02/18369, which is incorporated herein by reference in its entirety. In particular the disclosure relates to the treatment of HCV in patients infected with HIV comprising administering to a patient telaprevir.

[0008] One embodiment of the invention is a method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprising administering to the patient telaprevir alone or in combination with one or more of an anti-HIV agent, an interferon, or ribavirin.

[0009] Another embodiment of the invention is a therapeutic regimen comprising administering to a patient, infected with human immunodeficiency virus, telaprevir alone or in combination with one or more of an anti-HIV agent, an interferon, or ribavirin.

[0010] Another embodiment of the invention is a medicament comprising, separately or together, telaprevir, an anti-HIV agent optionally comprising an interferon, and/or ribavirin.

BRIEF DESCRIPTION OF THE FIGURES

[0011] FIG. 1 depicts the change in median trough plasma concentrations of tenofovir, efavirenz and atazanavir at 1, 2, 4, and 12 weeks after starting HCV treatment.

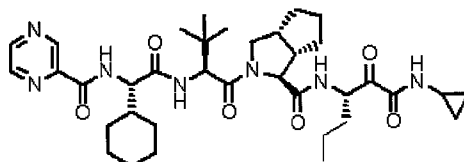
[0012] FIG. 2 depicts the median telaprevir concentrations by treatment arm.

[0013] FIG. 3 depicts the study design.

[0014] FIG. 4 depicts undetectable HCV RNA by treatment group: A. Week 4 (RVR); B. Week 12 (eVR); Weeks 4 and 12 (eRVR); and D. Week 24.

DETAILED DESCRIPTION

[0015] Telaprevir is described in PCT Publication Numbers WO 02/018369 and WO 2006/050250, and PCT Serial Number PCT/US2008/006572, filed on May 21, 2008, with reference to the



following structural formula, or a pharmaceutically acceptable salt thereof:

(I)

[0016] Other descriptions of telaprevir can be found in PCT Publication Numbers WO 07/098270 and WO 08/106151.

[0017] The efficacy of telaprevir in the treatment of HCV mono-infected patients was evaluated in two large Phase 2b clinical trials, PROVE 1 and PROVE 2. In these trials evaluating telaprevir was dosed in combination with pegylated interferon and ribavirin. The clinical trials showed that in 24-week telaprevir-based treatment regimens, genotype 1 treatment-naïve HCV patients achieved sustained viral response rates of 61% and 65% in PROVE 1 (SVR 12 and SVR 24) and PROVE 2 (SVR 12), respectively. In addition, clinical researchers reported a correlation between achieving rapid viral response (RVR) and achieving SVR in a 24-week telaprevir-based regimen. This is in contrast to HCV patients who undergo 48-week treatment regimens with currently approved therapies who achieve sustained viral response (SVR) in approximately 40% to 50% of people with genotype 1 hepatitis C. (See WO2010/093843, which is hereby incorporated in its entirety.)

[0018] Telaprevir has been tested in single doses in non-HIV infected humans and found to be well tolerated. The incidence or severity of adverse events did not increase with telaprevir dose. No adverse events were considered to be severe (grade 3 or grade 4). The more common and severe adverse events were skin adverse events (e.g., rash and pruritus), followed by gastrointestinal events and anemia. There were no clinically significant changes from baseline laboratory values for hematology or clinical chemistry parameters. There were no

clinically significant changes in physical examinations, vital signs, or electrocardiograms for any subject tested. (See WO2010/093843.)

- [0019] As used herein, “rapid virological response” or “RVR” is defined as undetectable HCV RNA 4 weeks after the end of therapy.
- [0020] As used herein, “complete early virologic response” or “cEVR” is defined as undetectable HCV RNA 12 weeks after the end of therapy.
- [0021] As used herein, “extended rapid virologic response” or “eRVR” is defined as undetectable HCV RNA at 4 and 12 weeks after the end of therapy.
- [0022] As used herein, “sustained virologic response” or “SVR” is defined as undetectable HCV RNA 24 weeks after the end of therapy.
- [0023] As used herein, “T” is an abbreviation for telaprevir.
- [0024] As used herein, “P” and “PegIFN-2a” are abbreviations for pegylated interferon-2a.
- [0025] As used herein, “R” and “RBV” are abbreviations for Ribavirin.
- [0026] As used herein, the term “HCV treatment naïve patient” refers to a patient who has not received any prior treatment for Hepatitis C.
- [0027] As used herein, the term “HIV treatment naïve patient” refers to a patient who has not received any prior treatment for HIV infection.
- [0028] As used herein, the singular forms “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise.
- [0029] Undetectable HCV RNA means that the HCV RNA is present in less than 10 IU/mL as determined by assays currently commercially available, for example, as determined by the Roche COBAS TaqMan™ HCV/HPS assay.
- [0030] The term “viral breakthrough” is defined by detectable HCV-RNA after achieving undetectable HCV-RNA during peg-IFN with RBV treatment. Specifically, viral breakthrough is defined as i) an increase in HCV RNA of $> 1\text{-log}_{10}$ compared to the lowest recorded on-treatment value or ii) an HCV RNA level of $> 100\text{ IU/mL}$ in a patient who had

undetectable HCV RNA at a prior time point. Specific examples of viral breakthrough responders include patients who have viral breakthroughs between week 4 and week 24.

- [0031] One embodiment of the invention is a method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprising administering to a patient telaprevir.
- [0032] In some embodiments, the method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprises administering to the patient telaprevir and an interferon.
- [0033] In one embodiment, the method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprises administering to the patient telaprevir and ribavirin.
- [0034] In another embodiment the method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprises administering to the patient telaprevir and an anti-HIV agent.
- [0035] In yet another embodiment, the method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprises administering to the patient telaprevir, an interferon and ribavirin.
- [0036] In still another embodiment the method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprises administering to the patient telaprevir, ribavirin and an anti-HIV agent.
- [0037] In another embodiment, the method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprises administering to the patient telaprevir, an interferon, and an anti-HIV agent.
- [0038] In still another embodiment, the method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprises administering to the patient telaprevir, an interferon, ribavirin and an anti-HIV agent.
- [0039] Another embodiment of the invention is a therapeutic regimen comprising administering to a patient, infected with human immunodeficiency virus, telaprevir.

- [0040] In some embodiments, the therapeutic regimen comprises administering to a patient, infected with human immunodeficiency virus, telaprevir and an interferon.
- [0041] In one embodiment, the therapeutic regimen comprises administering to a patient, infected with human immunodeficiency virus, telaprevir and ribavirin.
- [0042] In another embodiment, the therapeutic regimen comprises administering to a patient, infected with human immunodeficiency virus, telaprevir and an anti-HIV agent.
- [0043] In yet another embodiment, the therapeutic regimen comprises administering to a patient, infected with human immunodeficiency virus, telaprevir, an interferon and ribavirin.
- [0044] In some embodiments, the therapeutic regimen comprises administering to a patient, infected with human immunodeficiency virus, telaprevir, an interferon, and an anti-HIV agent.
- [0045] In yet other embodiments, the therapeutic regimen comprises administering to a patient, infected with human immunodeficiency virus, telaprevir, ribavirin, and an anti-HIV agent.
- [0046] In still another embodiment, the therapeutic regimen comprises administering to a patient, infected with human immunodeficiency virus, telaprevir, an interferon, ribavirin, and an anti-HIV agent.
- [0047] In some embodiments of the invention, the interferon is a pegylated interferon.
- [0048] In other embodiments, the interferon is a pegylated interferon alfa-2a.
- [0049] In still other embodiments, the interferon is a pegylated interferon alfa-2b.
- [0050] In some embodiments of the invention, the patient is a HCV treatment naïve patient.
- [0051] In some embodiments, the patient is a HIV treatment naïve patient.
- [0052] In some embodiments, the patient is both HCV treatment naïve and HIV treatment naïve.
- [0053] In some embodiments, telaprevir is administered in an amount of about 1000 to about 4000 mg/day.
- [0054] In some embodiments, telaprevir is administered in an amount of about 1500 to about 3500 mg/day.

- [0055] In some embodiments, telaprevir is administered in an amount of 750 mg three times per day.
- [0056] In some embodiments, telaprevir is administered in an amount of 750 mg twice per day.
- [0057] In some embodiments, telaprevir is administered in an amount of 1125 three times per day.
- [0058] In some embodiments, telaprevir is administered in an amount of 1125 twice per day.
- [0059] In some embodiments, telaprevir is administered every eight hours. In some embodiments, telaprevir is administered every twelve hours.
- [0060] In some embodiments, a pegylated interferon alfa-2a is administered in an amount of from about 50 μ g to about 180 μ g per week, e.g., about 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170 or 180 μ g per week.
- [0061] In certain embodiments, a pegylated interferon alfa-2a is administered in an amount of 180 μ g per week.
- [0062] In some embodiments, ribavirin is administered in an amount of from about 500 to 1500 mg per day, e.g., 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, or 1500 mg per day.
- [0063] In some embodiments, ribavirin is administered in an amount of 1200 mg per day.
- [0064] In some embodiments, ribavirin is administered in an amount of 800 mg per day.
- [0065] In some embodiments, ribavirin is administered in an amount of 600 mg per day.
- [0066] In some of the foregoing embodiments, the patient infected with human immunodeficiency virus, is administered a pegylated interferon alfa-2a, ribavirin and telaprevir, wherein a pegylated interferon alfa-2a, ribavirin and telaprevir are administered in an initial phase and a pegylated interferon alfa-2a and ribavirin are administered over a secondary phase, wherein the secondary phase occurs after the initial phase.
- [0067] In some of the foregoing embodiments, the patient infected with human immunodeficiency virus, is administered a pegylated interferon alfa-2a, ribavirin and telaprevir, wherein telaprevir is administered in an amount of 750 mg or 1125 mg every eight hours, pegylated a

alfa-2a is administered in an amount of 180 µg per week and ribavirin is administered in an amount of 1000 to 1200 mg per day.

- [0068] In some embodiments, the patient infected with human immunodeficiency virus, is administered a pegylated interferon alfa-2a, ribavirin and telaprevir, wherein telaprevir is administered in an amount of 1125 mg every eight hours, a pegylated alfa-2a is administered in an amount of 180 µg per week and ribavirin is administered in an amount of 600 or 800 mg per day.
- [0069] In some of the foregoing embodiments, the initial phase extends for a period of less than or about 24 weeks.
- [0070] In some of the foregoing embodiments, the initial phase extends for a period of about 12 weeks.
- [0071] In some of the foregoing embodiments, the secondary phase extends for a period of less than or about 24 weeks.
- [0072] In some foregoing embodiments, the secondary phase extends for a period of less than or about 36 weeks.
- [0073] In some of the foregoing embodiments, the secondary phase extends for a period of about 12 weeks.
- [0074] In some of the foregoing embodiments of the method, at least 40% of patients have undetectable HCV RNA levels at week 4. In some embodiments of the method, at least 50% of patients have undetectable HCV RNA levels at week 4. In some embodiments of the method, at least 60% of patients have undetectable HCV RNA levels at week 4. In some embodiments of the method, at least 70% of patients have undetectable HCV RNA levels at week 4.
- [0075] In some of the foregoing embodiments of the method, least 40% of patients have undetectable HCV RNA levels at week 12. In some embodiments of the method, at least 50% of patients have undetectable HCV RNA levels at week 12. In some embodiments of the method, at least 60% of patients have undetectable HCV RNA levels at week 12. In some embodiments of the method, at least 70% of patients have undetectable HCV RNA levels at week 12.

- [0076] Certain of the foregoing embodiments comprise the administration of an anti-HIV agent.
- [0077] In some embodiments, the anti-HIV agent is a nucleoside reverse transcriptase inhibitor, a nucleotide analog reverse transcriptase inhibitor, a non-nucleoside transcriptase inhibitor, a protease inhibitor, a fusion inhibitor, an entry inhibitor, an HIV integrase strand transfer inhibitor or a combination thereof.
- [0078] In some embodiments, the anti-HIV agent is abacavir sulfate, amprenavir, atazanavir sulfate, azidothymidine, darunavir, delaviridine mesylate, didanosine, efavirenz, emtricitabine, enfuvirtide, etravirine, fosamprenavir, fosamprenavir calcium, indinavir sulfate, lamivudine, lopinavir, maraviroc, nelfinavir mesylate, raltegravir, ritonavir, rilpivirine, nevirapine, saquinavir mesylate, stavudine, tenofovir disoproxil fumarate, tipranavir, zalcitabine, zidovudine, or a combination thereof.
- [0079] In other embodiments, the anti-HIV agent comprises efavirenz, tenofovir disoproxil fumarate, and emtricitabine.
- [0080] In other embodiments, the anti-HIV agent comprises etravirine, rilpivirine, or a combination thereof.
- [0081] In some embodiments, the anti-HIV agent comprises atazanavir sulfate and ritonavir.
- [0082] In some embodiments, the anti-HIV agent comprises raltegravir.
- [0083] In some embodiments, the anti-HIV agent comprises at least one reverse transcriptase inhibitor and at least one protease inhibitor.
- [0084] In certain embodiments, the anti-HIV agent is administered as HAART.
- [0085] In some embodiments, the anti-HIV agent is Atripla, Combivir, Emtriva, Epivir-HBV, Epzicom, Hivid, Retrovir, Trizivir, Truvada, Videx, Videx EC, Videxhaart, Viread, Zerit, or Ziagen.
- [0086] In some of the foregoing embodiments, the anti-HIV agent is administered before the administration of telaprevir.
- [0087] In some of the foregoing embodiments, the anti-HIV agent is administered concurrently with the administration of telaprevir.

- [0088] In some of the foregoing embodiments, the anti-HIV agent is administered after administration of telaprevir.
- [0089] Certain embodiments, according to this invention involve the treatment of a patient infected with genotype 1 Hepatitis C virus. Genotype 1 HCV infection is the most difficult strain of HCV to treat and the most prevalent strain in the United States.
- [0090] Another aspect of this invention involves treating or preventing one or more of liver damage, liver inflammation, steatosis, fatty liver, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatosis, and Reye's syndrome in a patient that is infected with HIV and either HCV positive or HCV negative.
- [0091] Also within the scope of this invention are methods for hepatoprotection in a patient that is either HCV positive or negative and is infected with HIV.
- [0092] The amounts of telaprevir according to this invention are administered in a single dosage form or in more than one dosage form. If in separate dosage forms, each dosage form is administered about simultaneously. For the avoidance of doubt, for dosing regimens calling for dosing more than once a day, one or more pill or dose may be given at each time per day (e.g., 1 pill, three times per day or 3 pills, three times per day). Most embodiments of this invention will employ at least 2 pills per dose).
- [0093] As would be realized by skilled practitioners, if a method of this invention is being used to treat a patient prophylactically, and that patient becomes infected with Hepatitis C virus, the method may then treat the infection. Therefore, one embodiment of this invention provides methods for treating or preventing a Hepatitis C infection in a patient infected with HIV.
- [0094] In addition to treating patients infected with Hepatitis C, the methods and therapeutic regimens of this invention may be used to prevent a patient from becoming infected with Hepatitis C. Accordingly, one embodiment of this invention provides a method for preventing a Hepatitis C virus infection in a patient infected with HIV comprising administering to the patient a composition or dosage form according to this invention.
- [0095] Methods and therapeutic regimens of this invention may also involve administration of another component comprising an additional agent selected from an immunomodulatory agent; an antiviral agent; an inhibitor of HCV protease (other than telaprevir); an inhibitor of another target in the HCV life cycle (other than NS3/4A protease); an inhibitor of internal

ribosome entry, a broad-spectrum viral inhibitor; or a cytochrome P-450 inhibitor; or combinations thereof. The additional agent is also selected from an inhibitor of viral cellular entry.

[0096] Accordingly, some embodiments, this invention comprise administering telaprevir and another anti-HCV agent. Such anti-HCV agents include, but are not limited to, immunomodulatory agents, such as α -, β -, and γ -interferons or thymosin, pegylated derivatized interferon- α compounds, and thymosin; other anti-viral agents, such as ribavirin, amantadine, and telbivudine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase, polymerase, and metalloprotease inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors (e.g., compounds described in U.S. Pat. No. 5,807,876, 6,498,178, 6,344,465, and 6,054,472; and PCT publications WO 97/40028, WO 98/40381, and WO 00/56331; and mycophenolic acid and derivatives thereof, and including, but not limited to, VX-497, VX-148, and VX-944); or any of their combinations.

[0097] Another embodiment of this invention provides a method or therapeutic regimen comprising administering telaprevir and a non-immunomodulatory or immunomodulatory agent. Such agents include, but are not limited to, those specified in WO 02/18369, which is incorporated herein by reference (see, e.g., page 273, lines 9-22 and page 274, line 4 to page 276, line 11 this disclosure being specifically incorporated herein by reference).

[0098] Still other agents include those described in various published U.S. Patent Applications. These publications provide additional teachings of compounds and methods that could be used in combination with telaprevir in the methods of this invention. It is contemplated that any such methods and compositions may be used in combination with the methods and compositions of the present invention. For brevity, the disclosure the disclosures from those publications is referred to be reference to the publication number but it should be noted that the disclosure of the compounds in particular is specifically incorporated herein by reference. Examples of such publications include U.S. Patent Application Publication Nos.: US 20040058982, US 20050192212, US 20050080005, US 20050062522, US 20050020503, US 20040229818, US 20040229817, US 20040224900, US 20040186125, US 20040171626, US 20040110747, US 20040072788, US 20040067901, US 20030191067, US 20030187018, US

20030186895, US 20030181363, US 20020147160, US 20040082574, US 20050192212, US 20050187192, US 20050187165, US 20050049220, and US 20050222236.

[0099] Still other agents include, but are not limited to, Albuferon™ (albumin-Interferon alpha) available from Human Genome Sciences; PEG-INTRON® (peginterferon alfa-2b, available from Schering Corporation, Kenilworth, NJ); INTRON-A®, (VIRAFERON®, interferon alfa-2b available from Schering Corporation, Kenilworth, NJ); ribavirin (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, CA; described in the Merck Index, entry 8365, Twelfth Edition); REBETROL® (Schering Corporation, Kenilworth, NJ); COPEGUS® (Hoffmann-La Roche, Nutley, NJ); PEGASYS® (peginterferon alfa-2a available Hoffmann-La Roche, Nutley, NJ); ROFERON® (recombinant interferon alfa-2a available from Hoffmann-La Roche, Nutley, NJ); BEREFOR® (interferon alfa 2 available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT); SUMIFERON® (a purified blend of natural alpha interferons such as Sumiferon available from Sumitomo, Japan); WELLFERON® (interferon alpha n1 available from Glaxo Wellcome Ltd., Great Britain); ALFERON® (a mixture of natural alpha interferons made by Interferon Sciences, and available from Purdue Frederick Co., CT); α-interferon; natural alpha interferon 2a; natural alpha interferon 2b; pegylated alpha interferon 2a or 2b; consensus alpha interferon (Amgen, Inc., Newbury Park, CA); REBETRON® (Schering Plough, Interferon-alpha 2B + Ribavirin); pegylated interferon alpha (Reddy, K.R. et al., "Efficacy and Safety of Pegylated (40-kd) Interferon alpha-2a Compared with Interferon alpha-2a in Noncirrhotic Patients with Chronic Hepatitis C," *Hepatology*, 33, 433-438 (2001); consensus interferon (INFERGEN®)(Kao, J.H., et al., "Efficacy of Consensus Interferon in the Treatment of Chronic Hepatitis," *J. Gastroenterol. Hepatol.*, 15, 1418-1423 (2000); lymphoblastoid or "natural" interferon; interferon tau (Clayette, P. et al., "IFN-tau, A New Interferon Type I with Antiretroviral activity" *Pathol. Biol. (Paris)* 47, 553-559 (1999); interleukin-2 (Davis, G.L. et al., "Future Options for the Management of Hepatitis C." *Seminars in Liver Disease*, 19, 103-112 (1999); Interleukin-6 (Davis et al., "Future Options for the Management of Hepatitis C," *Seminars in Liver Disease*, 19, 103-112 (1999); interleukin-12 (Davis, G.L. et al., "Future Options for the Management of Hepatitis C." *Seminars in Liver Disease*, 19, 103-112 (1999); and compounds that enhance the development of type 1 helper T cell response (Davis et al., "Future Options for the Management of Hepatitis C," *Seminars in Liver Disease*, 19, 103-112 (1999)). Also included are compounds that stimulate the synthesis of interferon in cells (Tazulakhova, E.B. et al.,

"Russian Experience in Screening, analysis, and Clinical Application of Novel Interferon Inducers" J. Interferon Cytokine Res., 21 65-73) including, but are not limited to, double stranded RNA, alone or in combination with tobramycin, and Imiquimod (3M Pharmaceuticals; Sauder, D.N. "Immunomodulatory and Pharmacologic Properties of Imiquimod," J. Am. Acad. Dermatol., 43 S6-11 (2000). See also, WO 02/18369, particularly page 272, line 15 to page 273, line 8, this disclosure being specifically incorporated herein by reference.

[00100] As is recognized by skilled practitioners, telaprevir is preferably administered orally. Interferon is not typically administered orally, although orally administered forms are in development. Nevertheless, nothing herein limits the methods or combinations of this invention to any specific dosage forms or regime. Thus, each component of a combination according to this invention may be administered separately, together, or in any combination thereof. As recognized by skilled practitioners, dosages of interferon are typically measured in IU (e.g., about 4 million IU to about 12 million IU). Interferon may also be dosed by micrograms. For example, a standard dose of Peg-Intron is 1.0-1.5 µg/kg/wk and of Pegasys is 180 µg/wk.

[00101] In some aspects, the method or therapeutic regimen includes the administration of agents over two phases, an initial phase and a secondary phase. For instance the initial phase can be a period of less than about 12 or 24 weeks and the secondary phase can be greater or equal to about 12 weeks, e.g., the secondary phase can be between about 12-36 weeks. In certain embodiments, the secondary phase is 12 weeks. In still other embodiments, the secondary phase is 36 weeks. In certain embodiments, the sum of the initial and secondary phase is about 24 to 48 weeks (such as 24, 36, or 48 weeks). In some embodiments, the initial and secondary phases can be identical in duration.

[00102] Telaprevir may be administered in either the initial, secondary, or both phases. In some embodiments, telaprevir is administered only in the initial phase. When telaprevir is administered only in the initial phase, telaprevir may be administered alone or in combination with other agents and one or more agents are administered in the secondary phase. The other agents can be one or more anti-HIV agents, one or more other agents described herein, or combinations thereof. In some embodiments, the specific agents administered in the initial and secondary phases are identical.

- [00103] In some embodiments, telaprevir is administered for 12 weeks (initial phase) followed by 12 weeks of administration of a combination of Peginterferon alfa-2a (Peg-IFN) and ribavirin (RBV) (secondary phase). In other embodiments, telaprevir is administered for 12 weeks (initial phase) followed by 24 weeks of administration of a combination of Peg-IFN and RBV (secondary phase). In other embodiments, telaprevir is administered for 12 weeks (initial phase) followed by 36 weeks of administration of a combination of Peg-IFN and RBV (secondary phase).
- [00104] In still other embodiments, telaprevir is administered for 12 weeks in combination with Peg-IFN (initial phase) followed by 12 weeks of administration of a combination of Peg-IFN and RBV (secondary phase). In other embodiments, telaprevir is administered for 12 weeks in combination with Peg-IFN (initial phase) followed by 24 weeks of administration of a combination of Peg-IFN and RBV (secondary phase). In other embodiments, telaprevir is administered for 12 weeks in combination with Peg-IFN (initial phase) followed by 36 weeks of administration of a combination of Peg-IFN and RBV (secondary phase).
- [00105] In still other embodiments, telaprevir is administered for 12 weeks in combination with Peg-IFN and RBV (initial phase) followed by 12 weeks of administration of a combination of Peg-IFN and RBV (secondary phase). In other embodiments, telaprevir is administered for 12 weeks in combination with Peg-IFN and RBV (initial phase) followed by 24 weeks of administration of a combination of Peg-IFN and RBV (secondary phase). In other embodiments, telaprevir is administered for 12 weeks in combination with Peg-IFN and RBV (initial phase) followed by 36 weeks of administration of a combination of Peg-IFN and RBV (secondary phase).
- [00106] In some embodiments, any of the initial phases described above can be conducted for about 12 weeks and the secondary phases can be conducted for about 12 weeks. Alternatively, the initial phase can be conducted for about 12 weeks and the secondary phase can be conducted for about 24 weeks. In still other aspects, the initial phase can be conducted for about 12 weeks and the secondary phase can be conducted for about 36 weeks.
- [00107] In some embodiments, any of the initial phases described above can be conducted for about 8 weeks and the secondary phases can be conducted for about 16 weeks. Alternatively, the initial phase can be conducted for about 8 weeks and the secondary phase can be conducted for about 28 weeks. In still other aspects, the initial phase can be conducted for about 8 weeks and the secondary phase can be conducted for about 40 weeks.

- [00108] In some embodiments, telaprevir is administered in combination with Peg-IFN for less than 48 weeks. For instance, in some embodiments telaprevir is administered in combination with Peg-IFN for less than 24 weeks.
- [00109] In some embodiments, telaprevir is administered in combination with Peg-IFN and RBV for less than 48 weeks. For instance, in some embodiments telaprevir is administered in combination with Peg-IFN and RBV for less than 24 weeks.
- [00110] Modeling data also indicate that telaprevir resistant variants, such as V36A/M, T54A, R155K/T, A156S A156V/T, V36A/M-R155K/T, and V36A/M-A156V/T, may be eradicated mainly by administering PEG-IFN and ribavirin for about 10-24 weeks (or 8-26 weeks) following telaprevir treatment. Certain of these regimens represent a reduction in treatment in the current standard of care treatment regimen lasting 24-48 weeks.
- [00111] In some embodiments, the patient is able to achieve week 4 RVR and week 12 undetectable status.
- [00112] Accordingly, this invention also provides methods or therapeutic regimens for administering telaprevir in combination with an interferon. In certain embodiments, the interferon is administered for about 10 weeks (or 10 weeks), about 12 weeks (or 12 weeks), about 14 weeks (or 14 weeks). Ribavirin is also optionally administered for all or part of the regimen, including but not limited to, the entire regimen.
- [00113] In one embodiment, a method or therapeutic regimen of this invention comprises administering a combination of telaprevir and Peg-IFN for about 12 weeks (or 12 weeks).
- [00114] In one embodiment, a method or therapeutic regimen of this invention comprises administering a combination of telaprevir and Peg-IFN for about 12 ± 4 weeks (e.g., 8, 12, or 16 weeks).
- [00115] In one embodiment, a method or therapeutic regimen of this invention comprises administering a combination of telaprevir and Peg-IFN for about 24 weeks (or 24 weeks).
- [00116] In one embodiment, a method or therapeutic regimen of this invention comprises administering a combination of telaprevir and Peg-IFN for about 24 ± 4 weeks (e.g., 20, 24, or 28 weeks).

- [00117] For the avoidance of doubt, it should be understood that this invention includes, but is not limited to, a regimen involving administering telaprevir and an interferon for about 8 weeks (or 8 weeks) followed by administering interferon for about 16 weeks (or 16 weeks) for a total treatment regimen of about 24 weeks (or 24 weeks). Also provided is a regimen involving administering telaprevir and an interferon for about 12 weeks (or 12 weeks) followed by administering interferon for about 12 weeks (or 12 weeks) for a total treatment regimen of about 24 weeks (or 24 weeks). Such regimens optionally provide administration of ribavirin for all or part of the regimen, including but not limited to, the entire regimen of about 24 weeks (or 24 weeks).
- [00118] In one embodiment, a method of this invention comprises administering a combination of telaprevir, Peg-IFN, and ribavirin for about 12 weeks (or 12 weeks).
- [00119] In one embodiment, a method of this invention comprises administering a combination of telaprevir, Peg-IFN, and ribavirin for about 12 weeks (or 12 weeks) followed by administering Peg-IFN and ribavirin for about 12 weeks (or 12 weeks).
- [00120] In one embodiment, a method of this invention comprises administering a combination of telaprevir, Peg-IFN, and ribavirin for about 12 weeks (or 12 weeks) followed by administering Peg-IFN and ribavirin for about 36 weeks (or 36 weeks).
- [00121] In one embodiment, a method of this invention comprises administering a combination of telaprevir, Peg-IFN, and ribavirin for about 24 weeks (or 24 weeks) followed by administering Peg-IFN and ribavirin for about 24 weeks (or 24 weeks).
- [00122] In some embodiments, the method includes providing a loading dose of telaprevir (1250 mg) followed by 750 mg q8h telaprevir plus a combination of Peg-IFN and RBV.
- [00123] In any of the foregoing embodiments, the administration of an anti-HIV agent, the timing of the administration of the anti-HIV agent may vary depending upon factors such as the severity of the HCV infection, or of the HIV infection. For example, where a patient has both advanced HIV disease and advanced HCV disease, it may be preferable to start HIV treatment before treatment with telaprevir. In some cases where HCV disease is mild, it may be preferable to delay treatment of the HCV. One of skill in the art would recognize that it is important to carefully select the particular anti-HIV regimen in order to reduce the risk of hepatotoxicity and interactions with HCV treatment. For example zidovudine increases the risk

of anemia form ribavirin. The National Institutes of Health publish and regularly update a publication: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, which provides detailed guidelines informative to the coordination of treatment for HIV and HCV in co-infected patients. One of skill in the art will recognize that the concepts relevant to HIV management evolve rapidly and such changes should be taken into account when choosing the correct treatment regimen.

[00124] One of skill in the art would recognize that alterations in dose or regimen may be recommended based on drug interactions studies or predicted interactions.

[00125] It is contemplated that the anti-HIV agent may be administered for all or part of the regimen, including but not limited to, the entire regimen. Thus, in some of the foregoing embodiments, the anti-HIV agent is administered prior to administration of telaprevir. In other embodiments, the anti-HIV agent is administered concurrently with the administration of telaprevir. In other embodiments, the anti-HIV agent is administered after the administration of telaprevir.

[00126] In some of the foregoing embodiments, the anti-HIV agent is administered before the initial phase.

[00127] In other of the foregoing embodiments, the anti-HIV agent is administered during the initial phase.

[00128] In yet other of the foregoing embodiments, the anti-HIV agent is administered during the secondary phase.

[00129] In other of the foregoing embodiments, the anti-HIV agent is administered after the secondary phase.

[00130] In other of the foregoing embodiments, the anti-HIV agent is administered during more than one phase. For example, the anti-HIV agent is administered before and during the initial phase, or the anti-HIV agent is administered during the initial phase and the secondary phase, or the anti-HIV agent is administered in the secondary phase and after the secondary phase. In some embodiments, the anti-HIV agent is administered in both the initial phase and the secondary phase.

- [00131] One embodiment of the invention is a medicament comprising, separately or together, telaprevir and an anti-HIV agent.
- [00132] In another embodiment, the medicament comprises, separately or together, telaprevir, an anti-HIV agent, and an interferon.
- [00133] In a further embodiment, the medicament comprises, separately or together, telaprevir, an anti-HIV agent, and a pegylated interferon. In another embodiment, the pegylated interferon is interferon alfa-2a. In another embodiment, the pegylated interferon is interferon alfa-2b.
- [00134] In another embodiment, the medicament comprises, separately or together, telaprevir, an anti-HIV agent, and ribavirin.
- [00135] In yet other embodiments, the medicament comprises, separately or together, telaprevir, an anti-HIV agent, a pegylated interferon, and ribavirin.
- [00136] In another embodiment the medicament comprises, separately or together, telaprevir, an anti-HIV agent a pegylated interferon alfa-2a, and ribavirin.
- [00137] In another embodiment the medicament comprises, separately or together, telaprevir, an anti-HIV agent, a pegylated interferon alfa-2b, and ribavirin.
- [00138] In some embodiments of the medicament, the anti-HIV agent is a nucleoside reverse transcriptase inhibitor, a nucleotide analog reverse transcriptase inhibitor, a non-nucleoside transcriptase inhibitor, a protease inhibitor, a fusion inhibitor, an entry inhibitor, an HIV integrase strand transfer inhibitor or a combination thereof.
- [00139] In some embodiments of the medicament, the anti-HIV agent is abacavir sulfate, amprenavir, atazanavir sulfate, azidothymidine, cobicistat, darunavir, delaviridine mesylate, didanosine, efavirenz, elvitegravir, emtricitabine, enfuvirtide, etravirine, fosamprenavir, fosamprenavir calcium, indinavir sulfate, lamivudine, lopinavir, maraviroc, nelfinavir mesylate, raltegravir, ritonavir, nevirapine, saquinavir mesylate, stavudine, tenofovir disoproxil fumarate, tipranavir, zalcitabine, zidovudine, or a combination thereof.
- [00140] In other embodiments of the medicament, the anti-HIV agent comprises efavirenz, tenofovir disoproxil fumarate, and emtricitabine.

- [00141] In some embodiments of the medicament, the anti-HIV agent comprises atazanavir sulfate and ritonavir.
- [00142] In some embodiments of the medicament, the anti-HIV agent comprises raltegravir.
- [00143] In some embodiments of the medicament, the anti-HIV agent comprises elvitegravir, cobicistat, tenofovir, and emtricitabine.
- [00144] In some embodiments of the medicament, the anti-HIV agent comprises etravirine, rilpivirine, or a combination thereof.
- [00145] In some embodiments of the medicament, the anti-HIV agent comprises at least one reverse transcriptase inhibitor and at least one protease inhibitor.
- [00146] In certain embodiments of the medicament, the anti-HIV agent is administered as HAART.
- [00147] In some embodiments of the medicament, the anti-HIV agent is Atripla, Combivir, Emtriva, Eпивir-HBV, Epzicom, Hivid, Retrovir, Trizivir, Truvada, Videx, Videx EC, Videxhaart, Viread, Zerit, or Ziagen..
- [00148] A cytochrome P450 monooxygenase ("CYP") inhibitor used in connection with this invention is expected to inhibit metabolism of anti-HIV agents. Therefore, the cytochrome P450 monooxygenase inhibitor would be in an amount effective to inhibit metabolism of the anti-HIV agent. Accordingly, the CYP inhibitor is administered in an amount such that the bioavailability of or exposure to the anti-HIV agent is increased in comparison to the anti-HIV agent in the absence of the CYP inhibitor. CYP inhibitors include, but are not limited to, ritonavir (WO 94/14436), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.
- [00149] Methods for measuring the ability of a compound to inhibit cytochrome P50 monooxygenase activity are known (see, U.S. Pat. No. 6,037,157, and Yun et al., *Drug Metabolism & Disposition*, 21, 403-407 (1993)). Methods for evaluating the influence of co-administration of telaprevir and a CYP inhibitor in a subject are also known (US

2004/0028755). Any such methods could be used in connection with this invention to determine the pharmacokinetic impact of a combination.

[00150] One embodiment of this invention provides a method for administering an inhibitor of CYP3A4 and an anti-HIV agent.

[00151] The methods herein may involve administration or co-administration of a) combinations of telaprevir and another agent; or b) telaprevir in more than one dosage form. Co-administration includes administering each inhibitor in the same dosage form or in different dosage forms. When administered in different dosage forms, the inhibitors may be administered at different times, including about simultaneously or in any time period around administration of the other dosage forms. Separate dosage forms may be administered in any order. That is, any dosage forms may be administered prior to, together with, or following the other dosage forms.

[00152] Telaprevir, and any additional agent, may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms administered to a patient, telaprevir, and any additional agent, may be formulated together in any combination. Any separate dosage forms may be administered at the same time or different times. It should be understood that dosage forms should be administered within a time period such that the biological effects were advantageous.

[00153] According to the regimens and dosage forms of this invention, telaprevir is present in an amount effective to decrease the viral load in a sample or in a patient, wherein said virus encodes a NS3/4A serine protease necessary for the viral life cycle (or in an amount effective to carry out a method of this invention), and a pharmaceutically acceptable carrier. Alternatively, a composition of this invention comprises an additional agent as described herein. Each component may be present in individual compositions, combination compositions, or in a single composition.

[00154] If pharmaceutically acceptable salts of compounds are utilized in these compositions, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentane-propionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-

hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth.

[00155] Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

[00156] The compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

[00157] Pharmaceutically acceptable carriers that may be used in these compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00158] According to a preferred embodiment, the compositions of this invention are formulated for pharmaceutical administration to a mammal, particularly a human being.

[00159] Formulations of telaprevir are described in PCT Publication Numbers WO 05/123076, WO 07/109604 and WO 07/109605, which are incorporated herein by reference in their entirety.

[00160] Such pharmaceutical compositions of the present invention (as well as compositions for use in methods, combinations, kits, and packs of this inventions) may be administered orally, parenterally, sublingually, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally or intravenously. More preferably, the compositions are administered orally.

[00161] Sterile injectable forms of the compositions of and according to this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00162] In compositions of this invention comprising telaprevir and an additional agent, telaprevir and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 to 80% of the dosage normally administered in a monotherapy regimen.

[00163] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, pills, powders, granules, aqueous suspensions or solutions. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added. Acceptable liquid dosage forms include emulsions, solutions, suspensions, syrups, and elixirs.

[00164] Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These may be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00165] The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00166] As is recognized in the art, pharmaceutical compositions may also be administered in the form of liposomes.

[00167] Applicants have demonstrated that telaprevir is orally bioavailable. Accordingly, preferred pharmaceutical compositions of this invention are formulated for oral administration.

[00168] For the CYP inhibitor, the dosage levels of between about 0.001 to about 200 mg/kg body weight per day, would be typical. More typical would be dosage levels of between about 0.1 to about 50 mg/kg or about 1.1 to about 25 mg/kg per day.

[00169] For preferred dosage forms of ritonavir, see U.S. Patent No. 6,037, 157, and the documents cited therein: U.S. Patent No. 5,484,801, U.S. Patent Application No. 08/402,690, and PCT Publications Nos. WO 95/07696 and WO 95/09614.

[00170] Administrations in connection with this invention can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to

produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

[00171] Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

[00172] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician and the severity of the particular disease being treated, prior treatment history, co-morbidities or concomitant medications, baseline viral load, race, duration of diseases, status of liver function and degree of liver fibrosis/cirrhosis, and the goal of therapy (eliminating circulating virus per-transplant or viral eradication). The amount of active ingredients will also depend upon the particular described compound and the presence or absence and the nature of the additional anti-HIV and/or anti-viral agent in the composition.

[00173] According to another embodiment, the invention provides a method for treating a patient infected with HIV and with a virus characterized by a virally encoded NS3/4A serine protease that is necessary for the life cycle of the virus by administering to said patient a pharmaceutically acceptable composition of this invention. Such treatment may completely eradicate the viral infection or reduce the severity thereof. Preferably, the patient is a mammal. More preferably, the patient is a human being.

[00174] Compositions comprising telaprevir, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle may be prepared e.g., by the methods disclosed in WO2010/093845. These compositions may also comprise additional agents.

- [00175] Pharmaceutical compositions may be prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.
- [00176] It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation, containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.
- [00177] According to a further aspect of the invention is a pack including telaprevir (in dosages according to this invention) and an information insert containing directions on the use of the combination of the invention. Any composition, dosage form, therapeutic regimen or other embodiment of this invention may be presented in a pharmaceutical pack. In an alternative embodiment of this invention, the pharmaceutical pack further comprises one or more of additional agent as described herein. The additional agent or agents may be provided in the same pack or in separate packs.
- [00178] Another aspect of this involves a packaged kit for a patient to use in the treatment of HCV infection or in the prevention of HCV infection in a patient infected with HIV (or for use in another method of this invention), comprising: a single or a plurality of pharmaceutical formulation of each pharmaceutical component; a container housing the pharmaceutical formulation(s) during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat or prevent HCV infection.
- [00179] Accordingly, this invention provides kits for the simultaneous or sequential administration of a dose of telaprevir (and optionally an additional agent). Typically, such a kit will comprise, e.g. a composition of each compound and optional additional agent(s) in a pharmaceutically acceptable carrier (and in one or in a plurality of pharmaceutical formulations) and written instructions for the simultaneous or sequential administration.
- [00180] In another embodiment, a packaged kit is provided that contains one or more dosage forms for self administration; a container means, preferably sealed, for housing the dosage forms

during storage and prior to use; and instructions for a patient to carry out drug administration. The instructions will typically be written instructions on a package insert, a label, and/or on other components of the kit, and the dosage form or forms are as described herein. Each dosage form may be individually housed, as in a sheet of a metal foil-plastic laminate with each dosage form isolated from the others in individual cells or bubbles, or the dosage forms may be housed in a single container, as in a plastic bottle. The present kits will also typically include means for packaging the individual kit components, i.e., the dosage forms, the container means, and the written instructions for use. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc.

[00181] A kit according to this invention could embody any aspect of this invention such as any composition, dosage form, therapeutic regimen, or pharmaceutical pack.

[00182] The packs and kits according to this invention optionally comprise a plurality of compositions or dosage forms. Accordingly, included within this invention would be packs and kits containing one composition or more than one composition.

[00183] In order that this invention to be more fully understood, the following preparative and testing examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1: Combination of Telaprevir with Peginterferon alfa-2a and Ribavirin in HIV/HCV Co-infected Patients.

[00184] Safety, viral kinetics and efficacy of treatment with telaprevir (TVR) and PegIFN alfa-2a/RBV in HIV/HCV genotype 1 coinfecting HCV treatment-naïve pts were investigated: Part A, no concurrent ART; Part B, stable, predefined ART.

[00185] 60 patients co-infected with HIV and HCV genotype 1, were enrolled. Overall, 88% were male, 69% were white, mean age was 46 years, 68% had genotype 1a HCV, 83% had baseline HCV RNA levels of >800,000 IU/mL and 10% had advanced fibrosis. The first group (the "TPR group") received telaprevir (T) at 750 mg or 1125 mg per 8 hours, PegIFN-2a (P) at 180 µg per week and Ribavirin (R) at 1000 mg or 1200 mg per day for 12 weeks followed by 36 weeks of PegIFN-2a (P) at 180 µg per week and Ribavirin (R) at 1000 mg or

1200 mg per day. The second group (the “control group”) received placebo, PegIFN-2a (P) at 180 µg per week and Ribavirin (R) at 1000 mg or 1200 mg per day for 48 weeks.

[00186] Two patients who received HAART in Part B experienced viral breakthrough.

Discontinuations due to adverse events occurred in two patients (3%) in the TPR groups versus 0 in the control groups. Pruritus, nausea, vomiting, pyrexia, anorexia and dizziness were more frequent in patients in the TPR group than in the control group. No cases of severe rash were observed. No significant changes in CD4 or HIV RNA levels were observed in part B patient who received either ART regimen.

[00187] Interim analysis was performed on 59 of the 60 enrolled patients after 40 treated patients had completed 8 weeks of dosing. The safety and tolerability of TPR was consistent with that observed in HCV mono-infected patients in previous studies; no novel adverse events were detected. RVR, cEVR and eRVR results are provided in Table 1.

Table 1

ART Treatment	Part A No ART		Part B Efavirenz/ Tenofovir/ Emtricitabine		Part B Atazanavir/ ritonavir		Total	
HCV Treatment	TPR n=7	Control n=6	TPR n=16	Control n=8	TPR n=14	Control n=8	TPR n=37	Control n=22
% (n) Undetectable HCV RNA* at week 4 (RVR)	71 (5)	0 (0)	75 (12)	12 (1)	64 (9)	0 (0)	70 (26)	0 (0)
% (n) Undetectable HCV RNA* at week 12 (cEVR)	71 (5)	17 (1)	75 (12)	12 (1)	57 (8)	12 (1)	68 (25)	14 (3)
% (n) Undetectable HCV RNA* at weeks 4 and 12 (eRVR)	43 (3)	0 (0)	62 (10)	0 (0)	43 (6)	0 (0)	49 (19)	0 (0)

*as determined by Roche Taqman® v2, LLOQ of 25 IU/mL

Example 2: Telaprevir in combination with Peginterferon alfa-2a and Ribavirin in HIV/HCV Co-infected Patients: A 24-Week Interim Analysis.

[00188] Safety, viral kinetics and efficacy of treatment with telaprevir (TVR) and PegIFN alfa-2a/RBV in HIV/HCV genotype 1 coinfecting HCV treatment-naïve pts were investigated. Part A: up to 20 patients not receiving ART, with CD4 count ≥ 500 cells/mm³, and HIV RNA $\leq 100,000$ copies/mL. Part B: up to 48 patients receiving a stable ART regimen: Efavirenz (EFV)/ Tenofovir (TDF)/ Emtricitabine (FTC), or Atazanavir (ATV)/ ritonavir (r) with TDF and FTC or lamivudine (3TC), with CD4 count ≥ 300 cells/mm³, and HIV RNA ≤ 50 copies/mL.

[00189] There were no HIV RNA breakthroughs. 3 T/PR patients experienced HCV RNA breakthrough: 1 receiving EFV/TDF/FTC and 1 receiving ATV/r + TDF/FTC at Week 4, and 1 receiving EFV/TDF/FTC at Week 12.

[00190] In this interim analysis, higher Week 24 on-treatment responses were seen in chronic genotype 1 HCV/HIV co-infected patients treated with T/PR (71%) compared to PR alone (55%) (Figure 4). TVR exposures were comparable across ART regimens. Overall safety and tolerability of patients treated with TVR combination treatment was comparable to that previously observed in chronic genotype 1 HCV-monoinfected patients. Hyperbilirubinemia was noted in patients receiving T/PR with an ATV/r-based regimen and was primarily unconjugated.

Table 2: Comparison of Telaprevir Steady-state Concentration by ART Regimens

Parameter	ART Drug Regimens	In HIV Co-infected Patients			
		Ref conc (no ART)	Conc Ratio to Ref (%)		
		Mean (ng/mL)	Mean	90% CILB	90% CIUB
C _{min}	EFV	1984	93	56	156
C _{min}	ATV/r	1984	131	77	222
C _{avg}	EFV	2830	97	64	146
C _{avg}	ATV/r	2830	107	70	165

C_{max}	EFV	3718	101	72	143
C_{max}	ATV/r	3718	98	69	140

EFV = efavirenz-based ART regimen

ATV/r = atazanavir/ritonavir-based ART regimen

Table 3: Pharmacokinetics of ART After and Before HCV Treatment in HIV/HCV Co-infected Patients

In HIV/HCV Co-infected Patients				
ART Medication	Median C_{min} before HCV treatment (ng/mL)		Median (10 th -90 th percentiles) ratio of C_{min} before and after HCV treatment*	
	+TVR/PR	+PBO/PR	+TVR/PR	+PBO/PR
Atazanavir (ATV)	1230	1890	122% (54% - Undef)	81% (16% - 220%)
Efavirenz (EFV)	1441	1925	86% (53% - 165%)	66% (52% - 148%)
Tenofovir (+EFV)	61.2	67.6	90% (60% - 422%)	59% (42% - 201%)
Tenofovir (-EFV)	128.1	139	83% (35% - 353%)	74% (53% - 170%)

EFV = efavirenz-based ART regimen

ATV = atazanavir/ritonavir-based ART regimen

OTHER EMBODIMENTS

[00191] While a number of embodiments and examples of this invention are described herein, it is apparent that these embodiments and examples may be altered to provide additional embodiments and examples which utilize the pharmaceutical formulations and drug regimens of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example above.

What is claimed is:

1. A method for treating, preventing, or managing hepatitis C virus infection in a patient infected with human immunodeficiency virus comprising administering to the patient telaprevir.
2. The method according to claim 1, further comprising administering an interferon.
3. The method according to claim 2, wherein the interferon is a pegylated interferon.
4. The method according to claim 3, wherein the interferon is a pegylated interferon alfa-2a.
5. The method according to claim 3, wherein the interferon is a pegylated interferon alfa-2b.
6. The method according to any of claims 1-5, further comprising administering ribavirin.
7. The method according to any one of claims 1-6, wherein the patient is a HCV treatment naïve patient.
8. The method according to any one of claims 1-7, wherein the patient is a HIV treatment naïve patient.
9. The method according to any one of claims 1-8, wherein telaprevir is administered in an amount of from about 1000 to about 4000 mg/day.
10. The method according to claim 9, wherein telaprevir is administered in an amount of from about 1500 to about 3500 mg/day.
11. The method according to claim 9, wherein telaprevir is administered in an amount of 750 mg three times per day.
12. The method according to claim 9, wherein telaprevir is administered in an amount of 750 mg twice per day.

13. The method according to claim 9, wherein telaprevir is administered in an amount of 1125 three times per day.
14. The method according to claim 9, wherein telaprevir is administered in an amount of 1125 twice per day.
15. The method according to claim 11 or 13, wherein telaprevir is administered every 8 hours.
16. The method according to claim 12 or 14, wherein telaprevir is administered every 12 hours.
17. The method of any one of claims 9-16, wherein the interferon is a pegylated interferon alfa-2a and is administered in an amount of 180 µg per week.
18. The method of any one of claims 9-17, wherein ribavirin is administered in an amount of from about 500 to about 1500 mg per day.
19. The method of claim 18, wherein ribavirin is administered in an amount of 1200 mg per day.
20. The method of claim 18, wherein ribavirin is administered in an amount of 800 mg per day.
21. The method of claim 18, wherein ribavirin is administered in an amount of 600 mg per day.
22. The method according to any one of claims 18-21, wherein the pegylated interferon alfa-2a, ribavirin and telaprevir are administered in an initial phase and the pegylated interferon alfa-2a and ribavirin are administered over a secondary phase, wherein the secondary phase occurs after the initial phase.
23. The method according to claim 22, wherein the secondary phase extends for a period of less than or about 36 weeks.
24. The method according to claim 22 or claim 23, wherein the initial phase extends for a period of less than or about 24 weeks.

25. The method according to claim 24, wherein the initial phase extends for a period of about 12 weeks.
26. The method according to any one of claims 23-25, wherein the secondary phase extends for a period of less than or about 24 weeks.
27. The method according to claim 26, wherein the secondary phase extends for a period of about 12 weeks.
28. The method according to any one of claims 1-27, wherein at least 40% of patients have undetectable HCV RNA levels at week 4.
29. The method according to claim 28, wherein at least 50% of patients have undetectable HCV RNA levels at week 4.
30. The method according to claim 29, wherein at least 60% of patients have undetectable HCV RNA levels at week 4.
31. The method according to claim 30, wherein at least 70% of patients have undetectable HCV RNA levels at week 4.
32. The method according to any one of claims 1-31, wherein at least 40% of patients have undetectable HCV RNA levels at week 12.
33. The method according to claim 32, wherein at least 50% of patients have undetectable HCV RNA levels at week 12.
34. The method according to claim 33, wherein at least 60% of patients have undetectable HCV RNA levels at week 12.
35. The method according to claim 34, wherein at least 70% of patients have undetectable HCV RNA levels at week 12.

36. The method according to any of claims 1-35, further comprising administering to the patient an anti-HIV agent.

37. The method according to claim 36, where the anti-HIV agent is a nucleoside reverse transcriptase inhibitor, a nucleotide analog reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, a fusion inhibitor, an entry inhibitor, an HIV integrase strand transfer inhibitor or a combination thereof.

38. The method according to claim 37, wherein the anti-HIV agent comprises at least one reverse transcriptase inhibitor and at least one protease inhibitor.

39. The method according to claim 36, wherein the anti-HIV agent is administered as HAART.

40. The method according to any one of claims 36-39, wherein the anti-HIV agent is administered before telaprevir.

41. The method according to any one of claims 36-39, wherein the anti-HIV agent is administered concurrently with telaprevir.

42. The method according to any one of claims 36-39, wherein the anti-HIV agent is administered after administration of telaprevir.

43. A therapeutic regimen comprising administering to a patient, infected with human immunodeficiency virus, telaprevir.

44. The therapeutic regimen according to claim 43, further comprising administering an interferon.

45. The therapeutic regimen according to claim 44, wherein the interferon is a pegylated interferon.

46. The therapeutic regimen according to claim 44, wherein the interferon is a pegylated interferon alfa-2a.

47. The therapeutic regimen according to claim 44, wherein the interferon is a pegylated interferon alfa-2b.

48. The therapeutic regimen according to any of claims 43-47, further comprising administering ribavirin.

49. The therapeutic regimen according to any one of claims 43-48, wherein the patient is a HCV treatment naïve patient.

50. The therapeutic regimen according to any one of claims 43-49, wherein the patient is a HIV treatment naïve patient.

51. The therapeutic regimen according to any one of claims 43-50, wherein telaprevir is administered in an amount of from about 1000 to about 4000 mg/day.

52. The therapeutic regimen according to claim 51, wherein telaprevir is administered in an amount of from about 1500-3500 mg/day.

53. The therapeutic regimen according to claim 51, wherein telaprevir is administered in an amount of 750 mg three times per day.

54. The therapeutic regimen according to claim 51, wherein telaprevir is administered in an amount of 750 mg twice per day.

55. The therapeutic regimen according to claim 51, wherein telaprevir is administered in an amount of 1125 three times per day.

56. The therapeutic regimen according to claim 51, wherein is administered in an amount of 1125 twice per day.

57. The method according to claim 53 or 55, wherein telaprevir is administered every 8 hours.

58. The method according to claim 54 or 56, wherein telaprevir is administered every 12 hours.

223306/VPI/11-104 WO/324229

59. The therapeutic regimen of any one of claims 51-58, in which wherein the pegylated interferon alfa-2a is administered in an amount of 180 µg per week.

60. The therapeutic regimen of any one of claims 51-59, in which wherein and ribavirin is administered in an amount of from about 500 to about 1500 mg per day.

61. The therapeutic regimen of claim 60, in which wherein and ribavirin is administered in an amount of 1200 mg per day.

62. The therapeutic regimen of claim 60, in which wherein and ribavirin is administered in an amount of 800 mg per day.

63. The therapeutic regimen of claim 60, in which wherein and ribavirin is administered in an amount of 600 mg per day.

64. The therapeutic regimen according to any one of claims 60-63, wherein the pegylated interferon alfa-2a, ribavirin and telaprevir are administered in an initial phase and the pegylated interferon alfa-2a and ribavirin are administered over a secondary phase, wherein the secondary phase occurs after the initial phase.

65. The therapeutic regimen according to claim 64, wherein the secondary phase extends for a period of less than or about 36 weeks.

66. The therapeutic regimen according to claim 64 or claim 65, wherein the initial phase extends for a period of less than or about 24 weeks.

67. The therapeutic regimen according to claim 66, wherein the initial phase extends for a period of about 12 weeks.

68. The therapeutic regimen according to any one of claims 65-67, wherein the secondary phase extends for a period of less than or about 24 weeks.

69. The therapeutic regimen according to claim 68, wherein the secondary phase extends for a period of about 12 weeks.

70. The therapeutic regimen according to any one of claims 43-69, wherein at least 40% of patients have undetectable HCV RNA levels at week 4.

71. The therapeutic regimen according to claim 70, wherein at least 50% of patients have undetectable HCV RNA levels at week 4.

72. The therapeutic regimen according to claim 71, wherein at least 60% of patients have undetectable HCV RNA levels at week 4.

73. The therapeutic regimen according to claim 72, wherein at least 70% of patients have undetectable HCV RNA levels at week 4.

74. The therapeutic regimen according to any one of claims 64-73, wherein at least 40% of patients have undetectable HCV RNA levels at week 12.

75. The therapeutic regimen according to claim 74, wherein at least 50% of patients have undetectable HCV RNA levels at week 12.

76. The therapeutic regimen according to claim 74, wherein at least 60% of patients have undetectable HCV RNA levels at week 12.

77. The therapeutic regimen according to claim 76, wherein at least 70% of patients have undetectable HCV RNA levels at week 12.

78. The therapeutic regimen according to any of claims 64-77, further comprising administering to the patient an anti-HIV agent.

79. The therapeutic regimen according to claim 78, where the anti-HIV agent is a nucleoside reverse transcriptase inhibitor, a nucleotide analog reverse transcriptase inhibitor, a non-nucleoside transcriptase inhibitor, a protease inhibitor, a fusion inhibitor, an entry inhibitor, an HIV integrase strand transfer inhibitor or a combination thereof.

80. The method according to claim 79, wherein the anti-HIV agent comprises at least one reverse transcriptase inhibitor and at least one protease inhibitor.

81. The therapeutic regimen according to claim 78, wherein the anti-HIV agent is administered as HAART.

82. The therapeutic regimen according to any one of claims 78-81, wherein the anti-HIV agent is administered before telaprevir.

83. The therapeutic regimen according to any one of claims 78-81, wherein the anti-HIV agent is administered concurrently with telaprevir.

84. The therapeutic regimen according to any one of claims 78-81, wherein the anti-HIV agent is administered after administration of telaprevir.

85. A medicament comprising, separately or together, telaprevir and an anti-HIV agent.

86. The medicament according to claim 85, further comprising, separately or together, an interferon.

87. The medicament according to claim 85, further comprising, separately or together, a pegylated interferon.

88. The medicament according to claim 85, further comprising, separately or together, a pegylated interferon alfa-2a

89. The medicament according to any one of claims 85-88, further comprising ribavirin.

90. The medicament according to any one of claims 85-89, wherein the anti-HIV agent is a nucleoside reverse transcriptase inhibitor, a nucleotide analog reverse transcriptase inhibitor, a non-nucleoside transcriptase inhibitor, a protease inhibitor, a fusion inhibitor, an entry inhibitor, an HIV integrase strand transfer inhibitor or a combination thereof.

91. The medicament according to any one of claims 85-89, wherein the anti-HIV agent is HAART.

┐

1/7

Change in Median Trough Plasma Concentrations After Start of T/PR

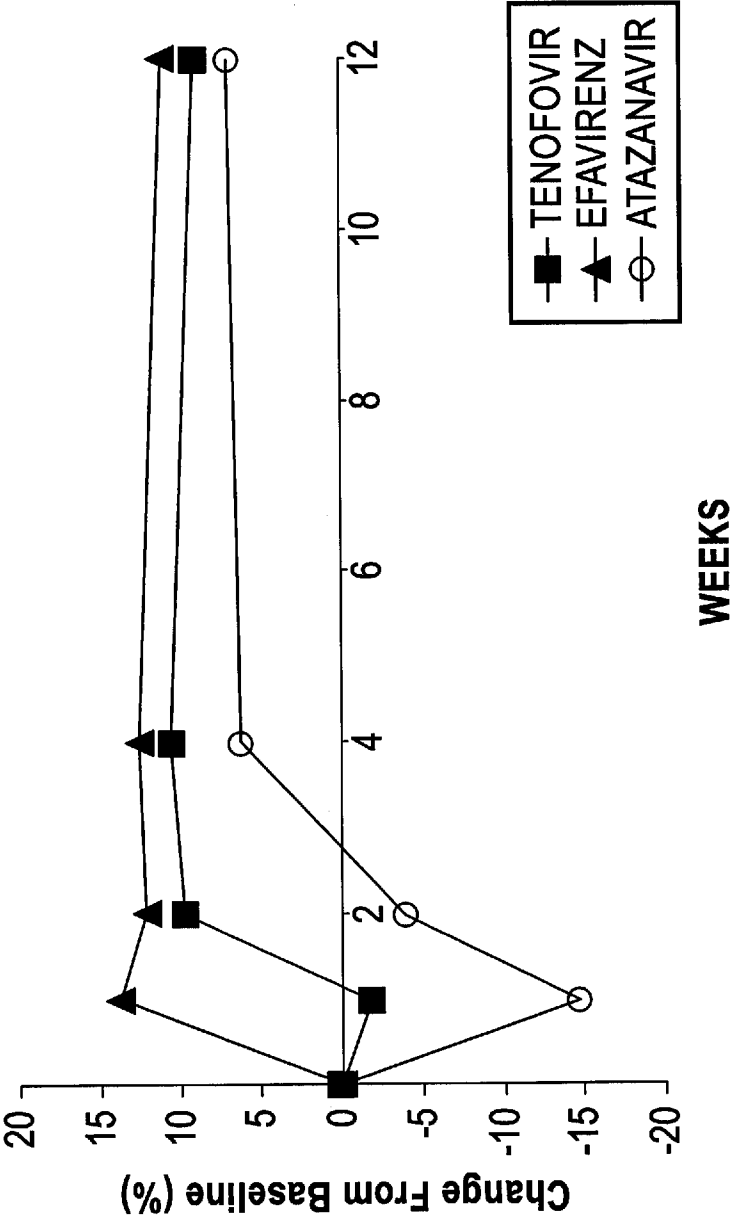


FIG. 1

┐

┌

2/7

Median Telaprevir Concentrations by Treatment Arm

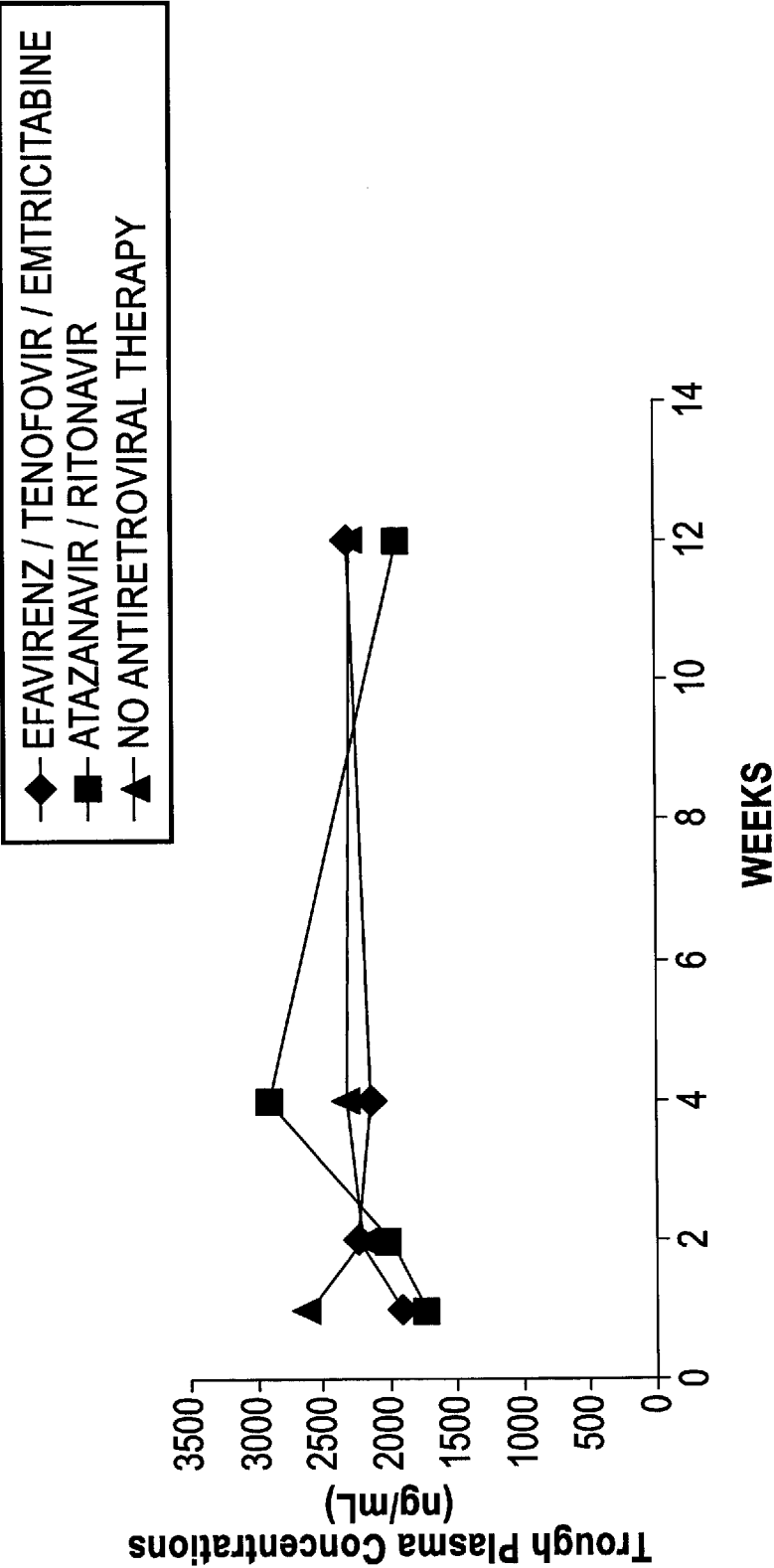


FIG. 2

┌

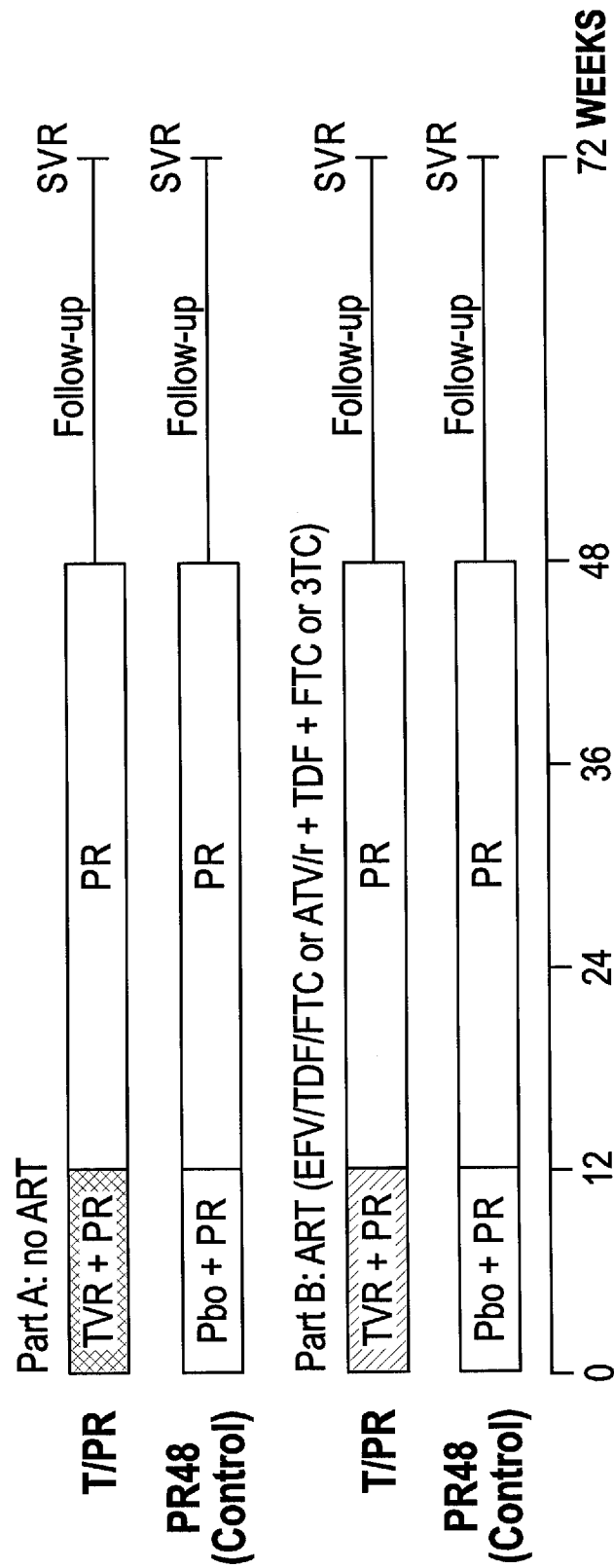


FIG. 3

└

4/7

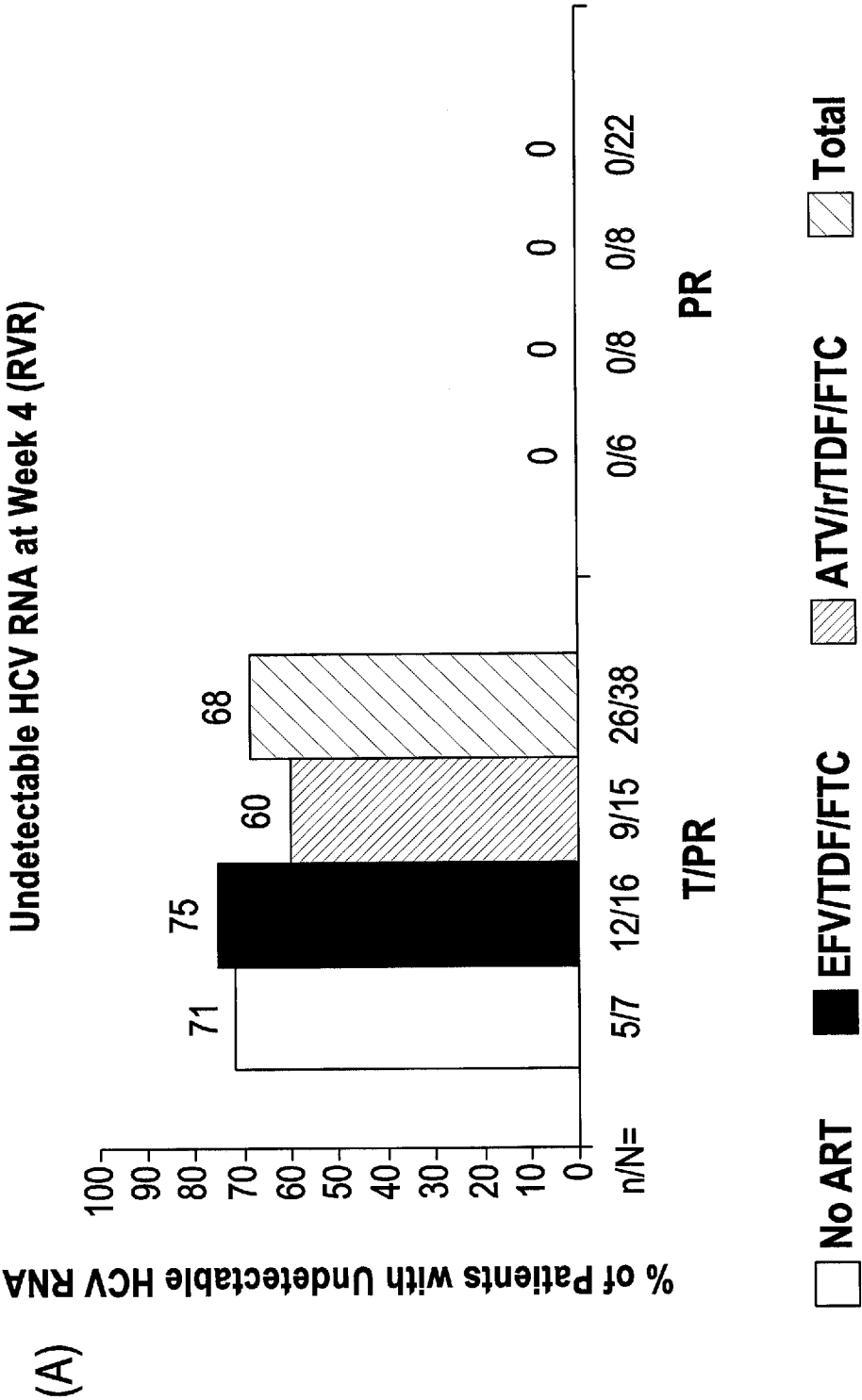


FIG. 4

└

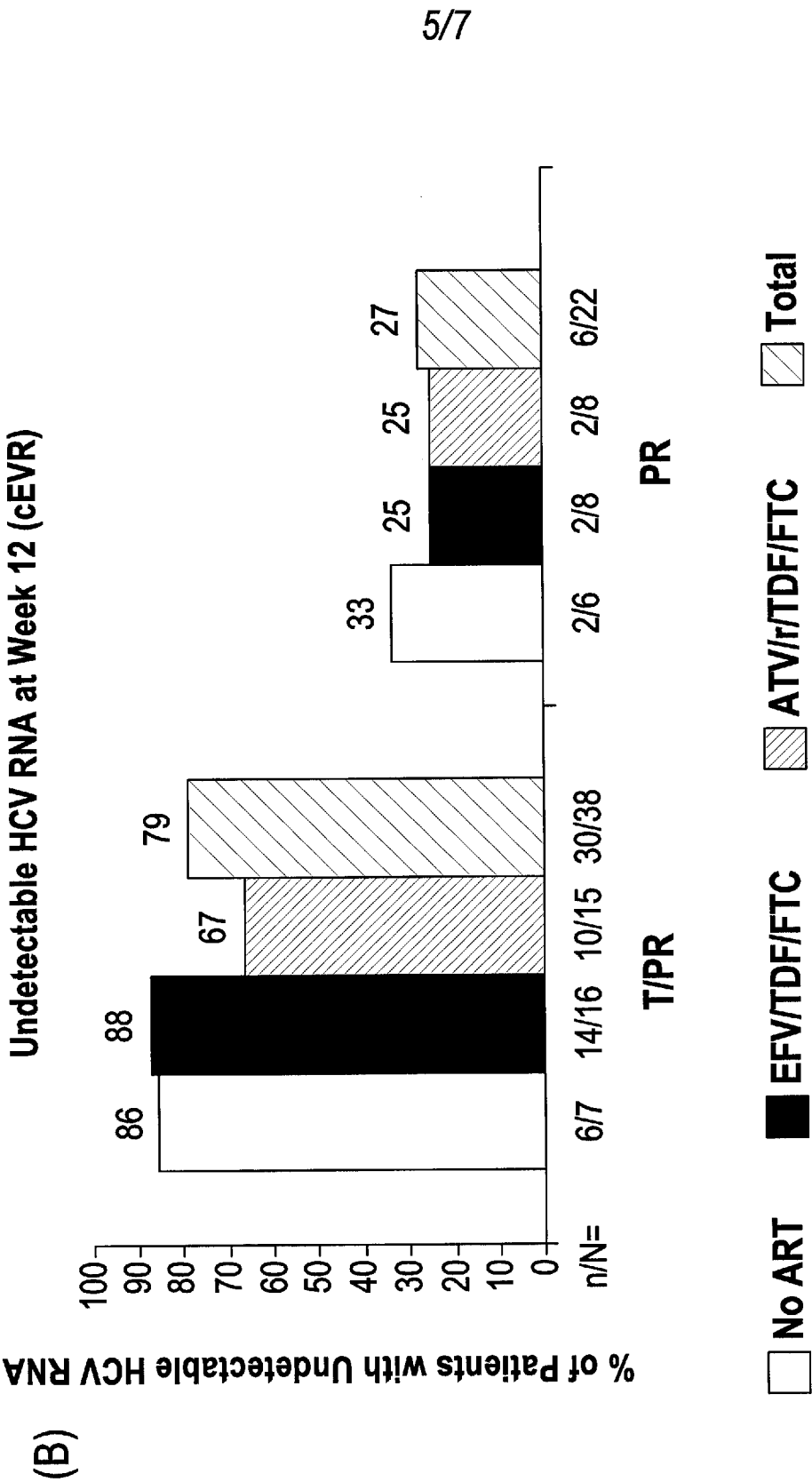


FIG. 4

┌

6/7

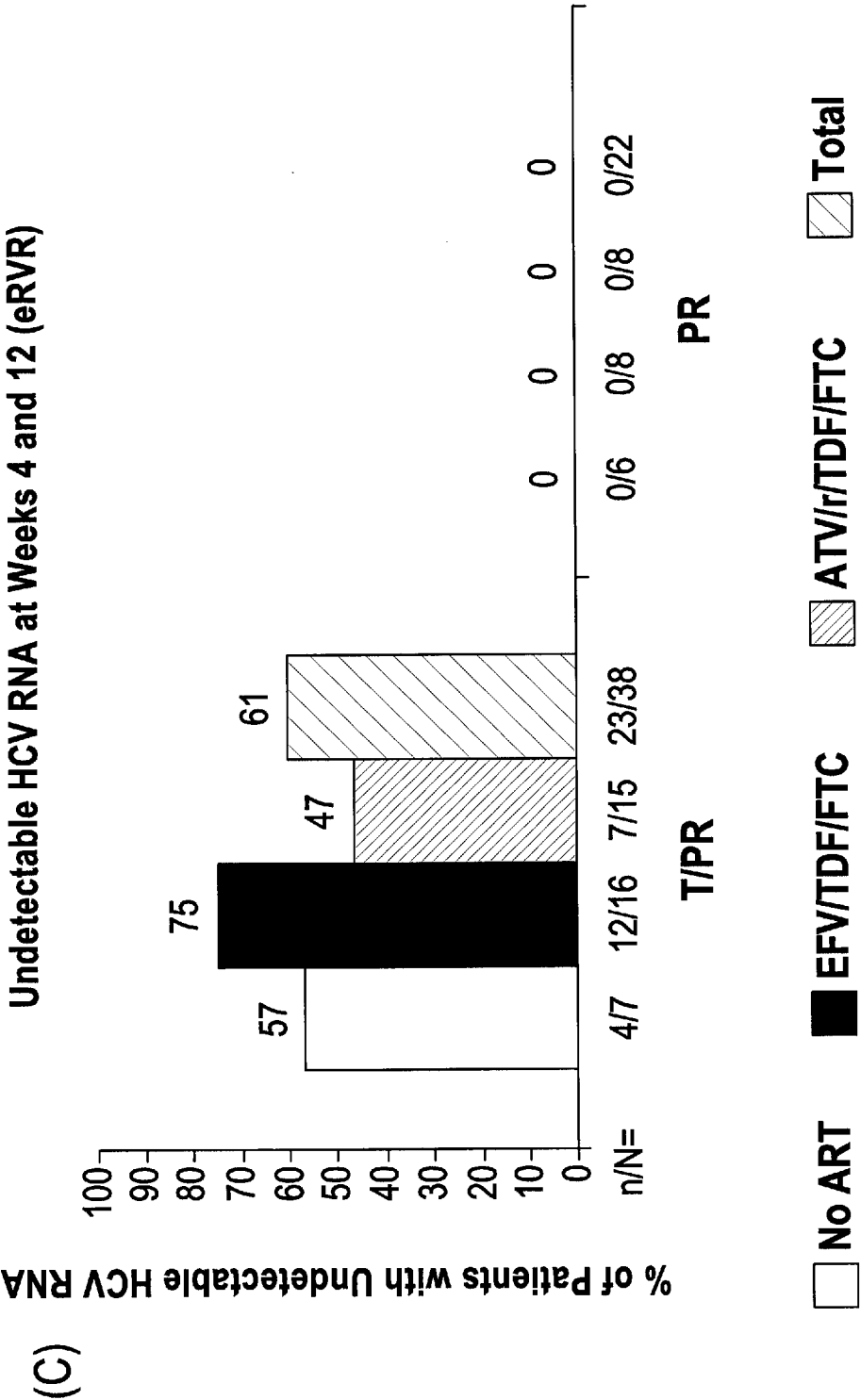


FIG. 4

└

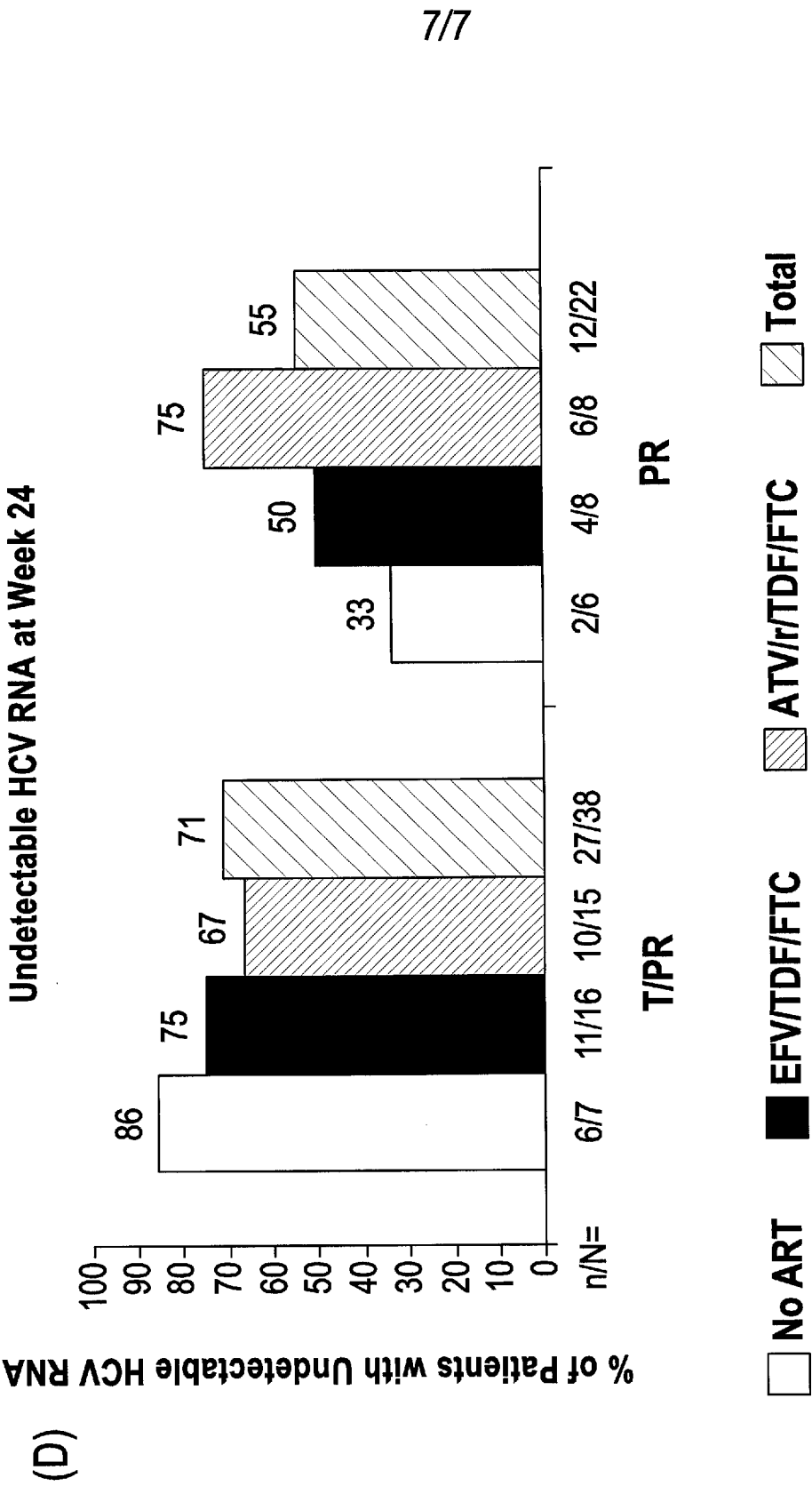


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/024850

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/497 A61K31/7056 A61K38/21 A61P31/12 A61P31/18 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, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHAEFER E ET AL: "HIV and HCV coinfection: Where are we in 2010?", CURRENT HEPATITIS REPORTS 2010 CURRENT SCIENCE, INC. USA LNKD- DOI:10.1007/S11901-010-0045-3, vol. 9, no. 3, August 2010 (2010-08), pages 155-160, XP002672331, ISSN: 1540-3416 See abstract, page 157 "Treatment of HIV-HCV coinfecting individuals": combination of peg-IFN and RBV as standard for treating mono and coinfecting individuals. See page 158 last paragraph, "the future" and page 159, first paragraph: telepravir added to peg-IFN and RBV therapy as immediate path forward for the treatment of HIV and HCV coinfecting patients; abstract -/--	1,7-16, 28-35, 43, 49-58, 70-77
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 26 March 2012		Date of mailing of the international search report 28/06/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Veronese, Andrea

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/024850

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	----- BARREIRO PABLO ET AL: "Prompt arrival of antivirals against hepatitis C for HIV patients.", AIDS REVIEWS 2010 OCT-DEC LNKD-PUBMED:21344779, vol. 12, no. 4, October 2010 (2010-10), pages 242-243, XP002672332, ISSN: 1698-6997 See page 242, figure and right hand column: telaprevir in combination with peg-IFN and ribavirin is very active against HCV virus infection. Clinical trials involving use of telaprevir to treat HIV-HCV coinfecting patients are expected	1,7-16, 28-35, 43, 49-58, 70-77
X	----- WO 2010/053942 A1 (VERTEX PHARMA [US]; HENSHAW JOSHUA [US]; GARG VARUN [US]; AHMAD ALAA M) 14 May 2010 (2010-05-14) See claims 1, 2, 13: telaprevir + interferon + ribavirin for the treatment of HCV patients	1,7-16, 28-35, 43, 49-58, 70-77
X	----- REVILL P ET AL: "Telaprevir: HCV NS3 protease inhibitor treatment of hepatitis C", DRUGS OF THE FUTURE, PROUS SCIENCE, ES, vol. 32, no. 9, 1 January 2007 (2007-01-01), pages 788-798, XP008095983, ISSN: 0377-8282, DOI: 10.1358/DOF.2007.032.09.1138229 Review: Telaprevir as a drug for the treatment of hepatitis C infection	1,7-16, 28-35, 43, 49-58, 70-77
X	----- AMOROSA VALERIANNA K: "New frontiers of HCV therapy in HIV/HCV co-infection.", CURRENT HIV/AIDS REPORTS AUG 2010 LNKD-PUBMED:20563864, vol. 7, no. 3, August 2010 (2010-08), pages 117-126, XP002672333, ISSN: 1548-3576 See page 117 and see page 121, last paragraph - page 122 NS3/4A "Protease inhibitors in HIV/HCV co-infection": clinical studies involving the use of telaprevir + peg-IFN + ribavirin in HIV-HCV co-infected patients -----	1,7-16, 28-35, 43, 49-58, 70-77

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/024850

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010053942 A1	14-05-2010	EP 2358439 A1	24-08-2011
		US 2011274652 A1	10-11-2011
		WO 2010053942 A1	14-05-2010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/024850

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 7-16, 28-35, 43, 49-58, 70-77(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 7-16, 28-35, 43, 49-58, 70-77(all partially)

Telaprevir alone, for use in the treatment of HIV-HCV
coinfected patients

2. claims: 1-84, 86-91(all partially)

Telaprevir in combination with the HCV agents interferon and
/ or ribavirin for use in the treatment of HIV-HCV
coinfected patients (in as far as not comprised in invention
1)

3. claim: 85

Telaprevir in combination with an HIV agent for use in the
treatment of HIV-HCV coinfectd patients (in as far as not
comprised in inventions 1 or 2)
