restore immunological control in the majority of patients. Accordingly, there is a need in the art for alternative therapies and combination therapies for subjects infected with HBV or having an HBV-associated disease.

SUMMARY ~~OF THE INVENTION~~

In one aspect, the present disclosure provides a double stranded ribonucleic acid (dsRNA) agent, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10) and the antisense strand comprises 5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16); wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively; Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (Agn) is adenosine-glycol nucleic acid (GNA); s is a phosphorothioate linkage; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the dsRNA agent as described herein and a pharmaceutical excipient. In another aspect, the present disclosure provides a method of inhibiting Hepatitis B virus (HBV) gene expression or inhibiting replication of a HBV in a cell *in vitro*, the method comprising contacting the cell with the dsRNA agent as described herein, or the pharmaceutical composition as described herein, thereby inhibiting expression or replication of the HBV gene in the cell. In still another aspect, the present disclosure provides use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for reducing the level of a Hepatitis B virus (HBV) antigen or reducing the viral load of HBV in a subject infected with HBV. In another aspect, the present disclosure provides use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating a subject having a Hepatitis B virus (HBV) infection. In another aspect, the present disclosure provides use of the dsRNA agent as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating a subject having a Hepatitis B virus (HBV)-associated disorder. In another aspect, the present disclosure provides the

dsRNA agent as described herein, or the pharmaceutical composition as described herein for use in therapy.

In some ~~embodiment~~examples, the present disclosure provides double stranded ribonucleic acid (dsRNA) agent compositions that affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a Hepatitis B virus (HBV) gene. The HBV gene may be within a cell, *e.g.*, a cell within a subject, such as a human.

The present disclosure also provides methods and therapies for treating a subject having a disorder that would benefit from inhibiting expression of an HBV gene, *e.g.*, an HBV infection or an HBV-associated disease, such as chronic Hepatitis B infection (CHB), using dsRNA agent compositions that affect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an HBV gene for inhibiting the expression of an HBV gene.

In one ~~aspect~~example, the present disclosure provides dsRNA agents for inhibiting expression of HBV. For example, the present disclosure provides a dsRNA agent comprising a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises the modified nucleotide sequence as set forth in:

5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16),
5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18),
5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20),
5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23),
5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24),
5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25), or
5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28),

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;

dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;

(Agn) is adenosine-glycol nucleic acid (GNA); and

s is a phosphorothioate linkage.

In some ~~embodiment~~examples, the sense strand comprises the modified nucleotide sequence 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29),

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; and

s is a phosphorothioate linkage.

In some ~~embodiment~~examples, the antisense strand and the sense strand comprise the modified nucleotide sequences as set forth in:

(a) 5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(b) 5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(c) 5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(d) 5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(e) 5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(f) 5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25) and 5'-gsusguGfcAfCfUfucgcuucaca -3' (SEQ ID NO:29); or

(g) 5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;

dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;

(Agn) is adenosine-glycol nucleic acid (GNA); and

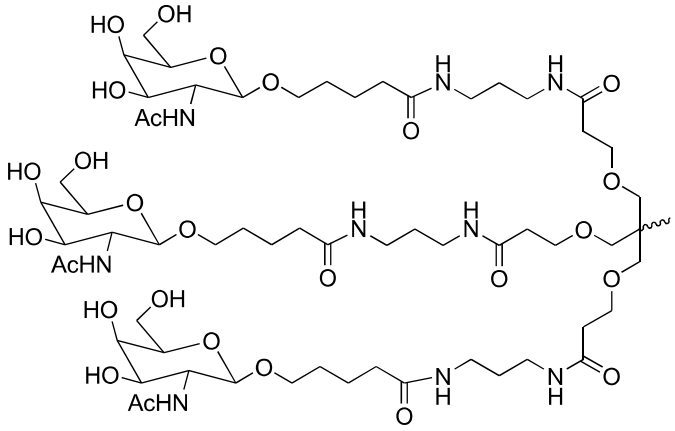
s is a phosphorothioate linkage.

In some ~~embodiment~~examples, at least one strand of the dsRNA agent comprises a 3' overhang of at least 1 nucleotide. In some ~~embodiment~~examples, at least one strand of the dsRNA agent comprises a 3' overhang of 2 nucleotides.

In some ~~embodiment~~examples, the double stranded region of the dsRNA agent is 19-21 nucleotide pairs in length.

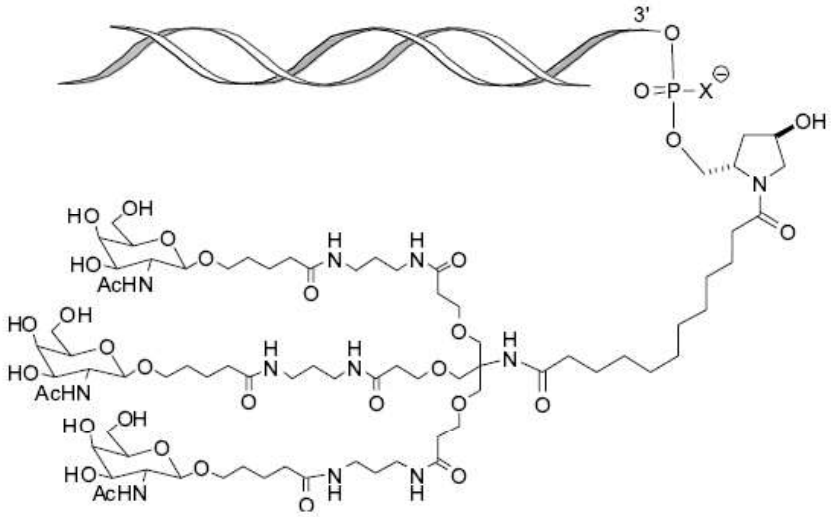
In some ~~embodiment~~examples, each strand of the dsRNA agent independently has 19-23 nucleotides. In some ~~embodiment~~examples, each strand of the dsRNA agent independently has 19-21 nucleotides.

In some ~~embodiment~~examples, dsRNA agent further comprises a ligand. In some ~~embodiment~~examples, the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent. In some ~~embodiment~~examples, the ligand is an N-acetylgalactosamine (GalNAc) derivative. In certain ~~embodiment~~examples, the ligand is



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In some ~~embodiment~~examples, the dsRNA agent is conjugated to the ligand as shown in the following schematic



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wherein X is O or S. In some ~~embodiment~~examples, the X is O.

In some ~~embodiment~~examples, the antisense strand consists of the modified nucleotide sequence as set forth in:

5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16),

5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18),

5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20),

5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23),

5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24),

5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25), or

5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28),

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;

dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;

(Agn) is adenosine-glycol nucleic acid (GNA); and

s is a phosphorothioate linkage.

In some ~~embodiment~~examples, the present disclosure provides a dsRNA agent, wherein the sense strand and the antisense strand consist of the modified nucleotide sequences as set forth in:

(a) 5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(b) 5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(c) 5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

(d) 5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23) and 5'-gsusguGfcAfCfUfucgcuucaca -3' (SEQ ID NO:29);

(e) 5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24) and 5'-gsusguGfcAfCfUfucgcuucaca -3' (SEQ ID NO:29);

(f) 5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25) and 5'-gsusguGfcAfCfUfucgcuucaca -3' (SEQ ID NO:29); or

(g) 5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;

dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;

(Agn) is adenosine-glycol nucleic acid (GNA);

s is a phosphorothioate linkage; and

the 3' end of the sense strand is conjugated to an N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol (L96) ligand.

In another aspect, the present disclosure also provides a cell containing a dsRNA agent as disclosed herein.

The present disclosure also provides a pharmaceutical composition comprising a dsRNA agent described herein and a pharmaceutical excipient.

The present disclosure also provides a method of inhibiting Hepatitis B virus (HBV) gene expression in a cell, the method comprising contacting the cell with a

dsRNA agent or a pharmaceutical composition as disclosed herein, thereby inhibiting expression of the HBV gene in the cell. In some ~~embodiment~~examples, the cell is within a subject. In some ~~embodiment~~examples, the subject is a human. In some ~~embodiment~~examples, the subject suffers from an HBV-associated disease. In some ~~embodiment~~examples the cell is *in vitro*. In some ~~embodiment~~examples, the HBV gene expression is inhibited by at least 80%, 90%, 95%, or 98%, or to below the level of detection of the assay method.

The present disclosure also provides a method of inhibiting replication of a Hepatitis B virus (HBV) in a cell, the method comprising contacting the cell with a dsRNA agent or a pharmaceutical composition as disclosed herein, thereby inhibiting replication of the HBV in the cell. In some ~~embodiment~~examples, the cell is within a subject. In some ~~embodiment~~examples, the subject is a human. In certain ~~embodiment~~examples, the subject suffers from an HBV-associated disease. In some ~~embodiment~~examples, the cell is *in vitro*. In certain ~~embodiment~~examples, replication of HBV in the cell is inhibited by at least 80%, 90%, 95%, or 98%, or to below the level of detection of the assay method.

Also provided herein is a method of reducing the level of a Hepatitis B virus (HBV) antigen in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition as disclosed herein, thereby reducing the level of the HBV antigen in the subject. In some ~~embodiment~~examples, the HBV antigen is HBsAg. In some ~~embodiment~~examples, the HBV antigen is HBeAg. In some ~~embodiment~~examples, the HBV antigen is measured in serum from a subject. In some ~~embodiment~~examples, the subject is HBeAg positive. In some ~~embodiment~~examples, the subject is HBeAg negative. In some ~~embodiment~~examples, the HBV antigen level is reduced in serum by at least 1 log10, at least 2 log10, at least 3 log10, or at least 4 log10; or to below the level of detection of the assay.

The present disclosure also provides a method of reducing the viral load of Hepatitis B virus (HBV) in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of a dsRNA agent or a pharmaceutical composition as disclosed herein, thereby reducing the viral load of HBV in the subject. In some ~~embodiment~~examples, the HBV viral load is measured in serum from a subject. In some ~~embodiment~~examples, the subject is HBeAg positive. In some ~~embodiment~~examples, the subject is HBeAg negative. In some ~~embodiment~~examples, the HBV viral load is reduced in serum by at least 1 log10, at least 2 log10, at least 3 log10, or at least 4 log10; or to below the level of detection of the assay.

Also provided herein is a method of treating a subject having a Hepatitis B virus (HBV) infection or an HBV-associated disorder, comprising administering to the subject a therapeutically effective amount of a dsRNA agent a pharmaceutical composition as disclosed herein, thereby treating the subject. In some ~~embodiment~~examples, the subject is HBeAg positive. In some ~~embodiment~~examples, the subject is HBeAg negative. In some ~~embodiment~~examples, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive. In some ~~embodiment~~examples, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.

In some ~~embodiment~~examples of the aforementioned methods, the dsRNA agent is administered to the subject at a dose of 0.01 mg/kg to 10 mg/kg, 0.5 mg/kg to 50 mg/kg, or 3 mg/kg to 10 mg/kg. In some ~~embodiment~~examples of the methods, the dsRNA agent is administered to the subject at a dose of 3 mg/kg to 10 mg/kg. In some ~~embodiment~~examples of the methods, the dsRNA agent is administered to the subject at a fixed dose of 50 mg to 200 mg.

In some ~~embodiment~~examples of the aforementioned methods, the dsRNA agent is administered to the subject subcutaneously.

In some ~~embodiment~~examples of the aforementioned methods, the dsRNA agent is administered to the subject in two or more doses.

In some ~~embodiment~~examples of the aforementioned methods, the dsRNA agent is administered to the subject once per month, once every two months, or once every three months. In some ~~embodiment~~examples of the methods, the dsRNA agent is administered to the subject no more than once per month.

In some ~~embodiment~~examples of the aforementioned methods, the method further comprises administering to the subject an additional therapeutic agent, *e.g.*, one or more additional therapeutic agents. An additional therapeutic agent can include, but is not limited to, an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, and a covalently closed circular (ccc) HBV DNA inhibitor, and a combination of any of the foregoing. In some ~~embodiment~~examples, the additional therapeutic agent is a reverse transcriptase inhibitor.

In some ~~embodiment~~examples, more than one additional therapeutic is administered, and the additional therapeutic agents are a reverse transcriptase inhibitor and an immune stimulator. A reverse transcriptase inhibitor can include, but is not limited to, Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, and AGX-1009. An immune stimulator can include, but is not limited to,

pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, and a Toll-like receptor 7 (TLR7) agonist.

Also provided herein are compositions for practicing any of the methods disclosed herein. In some ~~embodiment~~examples, the disclosure provides a dsRNA agent or a pharmaceutical composition as disclosed herein for use in the treatment of a Hepatitis B virus (HBV) infection in a subject. In some ~~embodiment~~examples, the present disclosure provides a dsRNA agent or a pharmaceutical composition as disclosed herein for use in the treatment of a Hepatitis B virus (HBV)-associated disorder in a subject. In some ~~embodiment~~examples, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive. In some ~~embodiment~~examples, the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative. In some ~~embodiment~~examples, the subject is being or has been administered an additional therapeutic agent, *e.g.*, an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, or a covalently closed circular (ccc) HBV DNA inhibitor, or a combination of any of the foregoing. In some ~~embodiment~~examples, the additional therapeutic agent is a reverse transcriptase inhibitor, *e.g.*, Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, or AGX-1009. In some ~~embodiment~~examples, the additional therapeutic agents being administered are a reverse transcriptase inhibitor (*e.g.*, Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, or AGX-1009) and an immune stimulator (*e.g.*, pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, or a Toll-like receptor 7 (TLR7) agonist).

The present disclosure provides for the use of a dsRNA agent or a pharmaceutical composition as disclosed herein, for practicing any of the aforementioned methods.

The present disclosure also provides for the use of a dsRNA agent as disclosed herein for the preparation or manufacture of a medicament for practicing any of the aforementioned methods.

The present disclosure also provides kits comprising a dsRNA agent or a pharmaceutical composition as disclosed herein, optionally with instructions for practicing a method described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 schematically depicts the structure of the approximately 3.2 kb double stranded HBV genome. Replication of the HBV genome occurs through an RNA intermediate and produces 4 overlapping viral transcripts (an about 3.5 kb transcript, an about 2.4 kb transcript, an about 2.1 kb transcript, and an about 0.7 kb transcript

CLAIMS

1. A double stranded ribonucleic acid (dsRNA) agent, comprising a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10) and the antisense strand comprises ~~the modified nucleotide sequence as set forth in:~~

5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16)~~,~~;
~~5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18),~~
~~5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20),~~
~~5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23),~~
~~5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24),~~
~~5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25), or~~
~~5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28),~~

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;

~~dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;~~

(Agn) is adenosine-glycol nucleic acid (GNA); ~~and~~

s is a phosphorothioate linkage; and

L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

~~2. The dsRNA agent of claim 1, wherein the sense strand comprises the modified nucleotide sequence 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29)~~

~~wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;~~

~~Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; and~~

~~s is a phosphorothioate linkage.~~

~~3. The dsRNA agent of claim 1, wherein the antisense strand and the sense strand comprise the modified nucleotide sequences as set forth in:~~

~~(a) 5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);~~

~~(b) 5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);~~

~~(c) 5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);~~

~~(d) 5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);~~

~~(e) 5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);~~

~~(f) 5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29); or~~

~~(g) 5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28) and 5'-gsusguGfcAfCfUfucgcuucaca-3' (SEQ ID NO:29);~~

~~wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;~~

~~Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;~~

~~dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;~~

~~(Agn) is adenosine-glycol nucleic acid (GNA); and~~

~~s is a phosphorothioate linkage.~~

4~~2~~. The dsRNA agent of ~~any claims 1-3~~claim 1, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

5~~3~~. The dsRNA agent of any one of claims 1-~~3~~2, wherein at least one strand comprises a 3' overhang of 2 nucleotides.

~~6. The dsRNA agent of any one of claims 1-5, wherein the double stranded region is 19-21 nucleotide pairs in length.~~

~~7. The dsRNA agent of any one of claims 1-6, wherein each strand independently has 19-23 nucleotides.~~

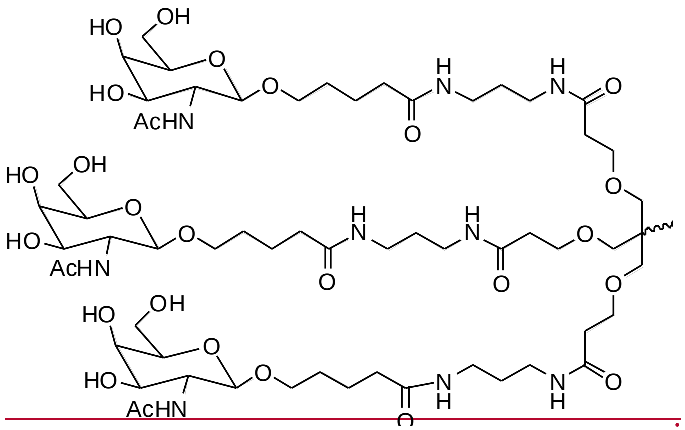
~~8. The dsRNA agent of claim 7, where each strand independently has 19-21 nucleotides.~~

~~9. The dsRNA agent of any one of claims 1-8, further comprising a ligand.~~

~~10. The dsRNA agent of claim 9, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA agent.~~

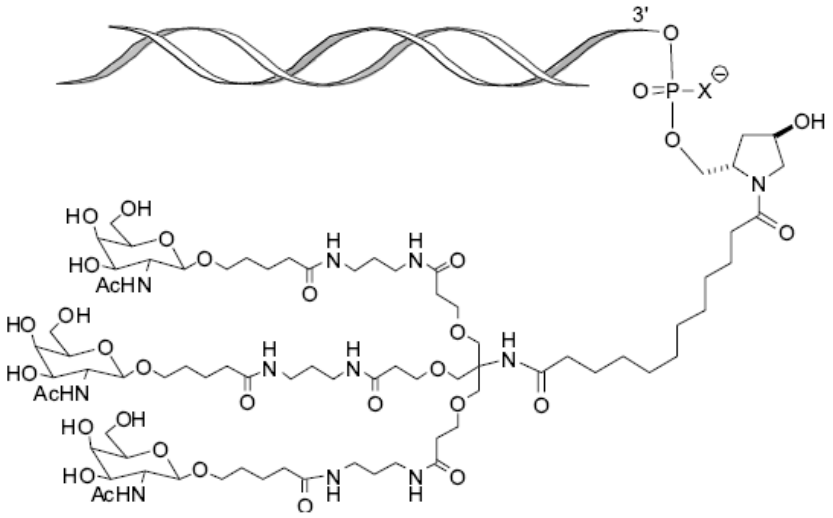
~~11. The dsRNA agent of claim 9 or 10, wherein the ligand is an N-acetylgalactosamine (GalNAc) derivative.~~

~~12. The dsRNA agent of claim 11, wherein the ligand is~~



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~~13~~4. The dsRNA agent of ~~claim 12~~any one of claims 1-3, wherein the ~~dsRNA agent~~L96 is conjugated to the ~~ligand~~3' end of the sense strand as shown in the following schematic



,

wherein X is O or S.

~~14~~5. The dsRNA agent of claim ~~13~~4, wherein the X is O.

~~15. The dsRNA agent of claim 1, wherein the antisense strand consists of the modified nucleotide sequence as set forth in:~~

~~5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16),~~

~~5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18),~~

~~5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20),~~

~~5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23),~~

~~5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24),~~

~~5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25), or~~

~~5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28),~~

~~wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;~~

~~Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;~~

dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;

(Agn) is adenosine-glycol nucleic acid (GNA); and

s is a phosphorothioate linkage.

16. The dsRNA agent of claim 1, wherein the antisense strand and the sense strand consist of the modified nucleotide sequences as set forth in:

(a) 5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10);

(b) 5'-usGfsuga(Agn)gcgaaguGfdCAfcacsusu-3' (SEQ ID NO:18) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10);

(c) 5'-usGfsudGa(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:20) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10);

(d) 5'-usGfsudGadAgdCGfaaguGfcAfcacsusu-3' (SEQ ID NO:23) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10);

(e) 5'-usGfsuga(Agn)dGCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:24) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10);

(f) 5'-usGfsudGadAgdCGfaaguGfcAfdCacsusu-3' (SEQ ID NO:25) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10); or

(g) 5'-usGfsuga(Agn)gCfGfaaguGfdCAfcacsusu-3' (SEQ ID NO:28) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10);

wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;

Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;

dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;

(Agn) is adenosine-glycol nucleic acid (GNA);

s is a phosphorothioate linkage; and

L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

17. The dsRNA agent of claim 1, wherein the antisense strand and the sense strand consist of the modified nucleotide sequences as set forth in:

5'-usGfsuga(Agn)gCfGfaaguGfcAfcacsusu-3' (SEQ ID NO:16) and 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO:10);

~~wherein a, c, g, and u are 2'-O-methyladenosine-3'-phosphate, 2'-O-methylcytidine-3'-phosphate, 2'-O-methylguanosine-3'-phosphate, and 2'-O-methyluridine-3'-phosphate, respectively;~~

~~Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;~~

~~dA, dC, dG, and dT are 2'-deoxyadenosine-3'-phosphate, 2'-deoxycytidine-3'-phosphate, 2'-deoxyguanosine-3'-phosphate, and 2'-deoxythymidine-3'-phosphate, respectively;~~

~~(Agn) is adenosine-glycol nucleic acid (GNA);~~

~~s is a phosphorothioate linkage; and~~

~~L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.~~

~~18~~6. The dsRNA agent of any one of claims 1-~~17~~5, wherein the dsRNA agent inhibits expression of hepatitis B virus (HBV) in a cell.

~~19~~7. A cell containing the dsRNA agent of any one of claims 1-~~18~~6.

~~20~~8. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-~~19~~ 6 and a pharmaceutical excipient.

~~21~~9. A method of inhibiting Hepatitis B virus (HBV) gene expression or inhibiting replication of a HBV in a cell *in vitro*, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-~~18~~6, or ~~a~~ the pharmaceutical composition of claim ~~20~~8, thereby inhibiting expression or replication of the HBV gene in the cell.

~~22~~10. The method of claim ~~21~~9, wherein the HBV gene expression or replication of HBV in the cell is inhibited by at least 80%, 90%, 95%, or 98%, or to below the level of detection of the assay method.

~~23. A method of inhibiting replication of a Hepatitis B virus (HBV) in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-18, or a pharmaceutical composition of claim 20, thereby inhibiting replication of the HBV in the cell.~~

~~24. The method of claim 23, wherein replication of HBV in the cell is inhibited by at least 80%, 90%, 95%, or 98%, or to below the level of detection of the assay method.~~

~~25. The method of any one of claims 21-24, wherein the cell is within a subject.~~

~~26. The method of claim 25, wherein the subject is a human.~~

~~27. The method of claim 26, wherein the subject suffers from an HBV-associated disease.~~

~~28. The method of any one of claims 21-24, wherein the cell is *in vitro*.~~

~~29~~11. ~~A method of reducing the level of a Hepatitis B virus (HBV) antigen in a subject infected with HBV, comprising administering to the subject a therapeutically effective amount of the~~ Use of the dsRNA agent of any one of claims 1-~~18~~6, or ~~a~~ the pharmaceutical composition of claim ~~20~~8, in the manufacture of a medicament for reducing the level of a Hepatitis B virus (HBV) antigen or reducing the viral load of HBV in a subject infected with HBV~~thereby reducing the level of the HBV antigen in the subject~~.

~~30~~12. The ~~method~~ use of claim ~~29~~11, wherein the HBV antigen is HBsAg or HBeAg.

~~31. The method of claim 29, wherein the HBV antigen is HBeAg.~~

~~32. The method of claim 29, wherein the antigen is measured in serum from the subject.~~

~~33. The method of claim 29, wherein the subject is HBeAg positive.~~

~~34. The method of claim 29, wherein the subject is HBeAg negative.~~

~~35~~13. The ~~method~~use of any one of claims ~~29-34~~11-12, wherein the HBV antigen level is reduced in serum by at least 1 log10, at least 2 log10, at least 3 log10, or at least 4 log10; or to below the level of detection of the assay.

~~36. A method of reducing the viral load of Hepatitis B virus (HBV) in a subject infected with HBV, comprising administering to the subject a therapeutically effective~~

~~amount of the dsRNA agent of any one of claims 1-18, or a pharmaceutical composition of claim 20, thereby reducing the viral load of HBV in the subject.~~

~~37. The method of claim 36, wherein the HBV viral load is measured in serum from the subject.~~

~~38. The method of claim 36 or 37, wherein the subject is HBeAg positive.~~

~~39. The method of claim 36 or 37, wherein the subject is HBeAg negative.~~

~~40~~14. The ~~method~~use of ~~any one of claims 36-39~~claim 11, wherein the HBV viral load is reduced in serum by at least 1 log10, at least 2 log10, at least 3 log10, or at least 4 log10; or to below the level of detection of the assay.

15. The use of any one of claims 11-14, wherein the subject is HBeAg positive.

16. The use of any one of claims 11-14, wherein the subject is HBeAg negative.

~~41~~17. ~~A method of treating a subject having a Hepatitis B virus (HBV) infection, comprising administering to the subject a therapeutically effective amount of the~~ Use of the dsRNA agent of any one of claims 1-~~18~~6, or ~~a~~ the pharmaceutical composition of claim ~~20~~8, in the manufacture of a medicament for treating a subject having a Hepatitis B virus (HBV) infection~~thereby treating the subject~~.

~~42~~18. ~~A method of treating a subject having a Hepatitis B virus (HBV)-associated disorder, comprising administering to the subject a therapeutically effective amount of the~~ Use of the dsRNA agent of any one of claims 1-~~18~~6, or a pharmaceutical composition of claim ~~20~~8, in the manufacture of a medicament for treating a subject having a Hepatitis B virus (HBV)-associated disorder~~thereby treating the subject~~.

~~43~~19. The ~~method~~use of claim ~~42~~18, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive.

~~44~~20. The ~~method~~use of claim ~~42~~18, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.

~~45~~21. The ~~method~~use of any one of claims ~~21-44~~11-20, wherein the dsRNA agent is to be administered to the subject at a dose of 0.01 mg/kg to 10 mg/kg, 0.5 mg/kg to 50 mg/kg, or 3 mg/kg to 10 mg/kg.

~~46. The method of claim 45, wherein the dsRNA agent is administered to the subject at a dose of 3 mg/kg to 10 mg/kg.~~

~~47~~22. The ~~method~~use of any one of claims ~~21-44~~11-20, wherein the dsRNA agent is to be administered to the subject at a fixed dose of 50 mg to 200 mg or 50 to 900 mg.

~~48~~23. The ~~method~~use of any one of claims ~~21-47~~11-22, wherein the dsRNA agent is to be administered to the subject subcutaneously.

~~49~~24. The ~~method~~use of any one of claims ~~21-48~~11-23, wherein the dsRNA agent is to be administered to the subject in two or more doses.

~~50~~25. The ~~method~~use of any one of claims ~~21-49~~11-24, wherein the dsRNA agent is to be administered to the subject once per month, once every two months, or once every three months.

~~51. The method of any one of claims 21-49, wherein the dsRNA agent is administered to the subject no more than once per month.~~

~~52~~26. The ~~method~~use of any one of claims ~~21-51~~11-25, ~~further comprising administering to~~wherein the subject is to be or has been administered one or more additional therapeutic agents.

~~53~~27. The ~~method~~use of claim ~~52~~26, wherein the additional therapeutic agent is an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, or a covalently closed circular (ccc) HBV DNA inhibitor, or a combination of any of the foregoing.

~~54~~28. The ~~method~~ use of claim ~~52~~26, wherein the additional therapeutic agent is a reverse transcriptase inhibitor.

~~55~~29. The ~~method~~ use of claim ~~52~~26, wherein the additional therapeutic agents are a reverse transcriptase inhibitor and an immune stimulator.

~~56~~30. The ~~method~~use of claim ~~54~~ 28 or ~~55~~29, wherein the reverse transcriptase inhibitor is Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, or AGX-1009.

~~57~~31. The ~~method~~use of claim ~~55~~29, wherein the immune stimulator is pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, or a Toll-like receptor 7 (TLR7) agonist.

~~58. A pharmaceutical composition for practicing any of the methods of any one of claims 21-57 comprising a dsRNA agent of any of claims 1-18 and a pharmaceutical excipient.~~

~~59. A dsRNA agent of any one of claims 1-18, or a pharmaceutical composition of claim 20, for use in the treatment of a Hepatitis B virus (HBV) infection in a subject.~~

~~60. A dsRNA agent of any one of claims 1-18, or a pharmaceutical composition of claim 20, for use in the treatment of a Hepatitis B virus (HBV) associated disorder in a subject.~~

~~61. The dsRNA agent or pharmaceutical composition for use according to claim 60, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg positive.~~

~~62. The dsRNA agent or pharmaceutical composition for use according to claim 60, wherein the HBV-associated disorder is chronic hepatitis and the subject is HBeAg negative.~~

~~63. The dsRNA agent or pharmaceutical composition for use according to any one of claims 59-62, wherein the subject is being or has been administered one or more additional therapeutic agents.~~

~~64. The dsRNA agent or pharmaceutical composition for use according to claim 63, wherein the additional therapeutic agent is an antiviral agent, a reverse transcriptase inhibitor, an immune stimulator, a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, or a covalently closed circular (ccc) HBV DNA inhibitor, or a combination of any of the foregoing.~~

~~65. The dsRNA agent or pharmaceutical composition for use according to claim 63, wherein the additional therapeutic agent is a reverse transcriptase inhibitor.~~

~~66. The dsRNA agent or pharmaceutical composition for use according to claim 63, wherein the additional therapeutic agents are a reverse transcriptase inhibitor and an immune stimulator.~~

~~67. The dsRNA agent or pharmaceutical composition for use according to claim 65 or 66, wherein the reverse transcriptase inhibitor is Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, or AGX-1009.~~

~~68. The dsRNA agent or pharmaceutical composition for use according to claim 66, wherein the immune stimulator is pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, or a Toll-like receptor 7 (TLR7) agonist.~~

~~69. Use of a dsRNA agent of any one of claims 1-18, or a pharmaceutical composition of claim 20 for practicing any of the methods of any one of claims 21-57.~~

~~70. Use of a dsRNA agent of any one of claims 1-18, or a pharmaceutical composition of claim 20, for the preparation of a medicament for practicing any of the methods of any one of claims 21-57.~~

32. The dsRNA agent of any one of claims 1-6, or the pharmaceutical composition of claim 8 for use in therapy.