Summary

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a Hepatitis D virus (HDV) gene. The HDV gene may be within a cell, *e.g.,* a cell within a subject, such as a human. In one aspect, the present invention refers to a double stranded RNAi agent for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand and said antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sense and antisense strands of SEQ ID NO: 1963, SEQ ID NO: 2141, SEQ ID NO: 1935, SEQ ID NO: 2113, SEQ ID NO: 1952, SEQ ID NO: 2130, SEQ ID NO: 1947, SEQ ID NO: 2125, SEQ ID NO: 1975, SEQ ID NO: 2153, SEQ ID NO: 1931, SEQ ID NO: 2109, SEQ ID NO: 1958, SEQ ID NO: 2136, SEQ ID NO: 1981, SEQ ID NO: 2159, SEQ ID NO: 1998, SEQ ID NO: 2176, SEQ ID NO: 1863, SEQ ID NO: 2041, SEQ ID NO: 1874, SEQ ID NO: 2052, SEQ ID NO: 1862, SEQ ID NO: 2040, SEQ ID NO: 1865, SEQ ID NO: 2043, SEQ ID NO: 1871, SEQ ID NO: 2049, SEQ ID NO: 1873, SEQ ID NO: 2051, SEQ ID NO: 1962, SEQ ID NO: 2140, SEQ ID NO: 1970, SEQ ID NO: 2148, SEQ ID NO: 1974, SEQ ID NO: 2152, SEQ ID NO: 1971, SEQ ID NO: 2149, SEQ ID NO: 1972, SEQ ID NO: 2150, SEQ ID NO: 1959, SEQ ID NO: 2137, SEQ ID NO: 1960, SEQ ID NO: 2138, SEQ ID NO: 1978, and SEQ ID NO: 2156. In another aspect, the present invention refers to a composition comprising two or more double stranded RNAi agents of the present invention for inhibiting expression of hepatitis D virus (HDV) in a cell. In yet another aspect, the present invention refers to a composition for inhibiting expression of hepatitis D virus (HDV) in a cell, said composition comprising: (a) a first double-stranded RNAi agent comprising an RNAi agent of the present invention, wherein not more than 5, 4, 3, 2, or 1 of the nucleotides of said first sense strand and not more than 5, 4, 3, 2, or 1 of the nucleotides of said first antisense strand are unmodified nucleotides, wherein said first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising an RNAi agent according to claim 7, wherein not more than 5, 4, 3, 2, or 1 of the nucleotides of said second sense strand and not more than 5, 4, 3, 2, or 1 of the nucleotides of said second antisense strand are unmodified nucleotides, wherein said second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. In one aspect, the present invention refers to a pharmaceutical composition comprising the double stranded RNAi agent of the present invention, or the composition of the

present invention. In one aspect, the present invention refers to an *in vitro* method of inhibiting Hepatitis D virus (HDV) gene expression or replication in a cell, the method comprising: (a) contacting the cell with the double stranded RNAi agent of the present invention, the composition of the present invention; and (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of an HDV gene, thereby inhibiting expression or replication of the HDV gene in the cell. In one aspect, the present invention refers to the use of the double stranded RNAi agent of the present invention, or the composition of the present invention, or the pharmaceutical composition of the present invention in the manufacture of a medicament for treating a subject having a Hepatitis D virus (HDV) infection.

The present disclosure also provides methods and therapies for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of an HDV gene, *e.g.,* an HDV infection and/or an HDV-associated disease, such as hepatitis B virus infection, chronic hepatitis B infection (CHB), chronic Hepatitis D infection (CHD), cirrhosis, liver failure, and hepatocellular carcinoma (HCC), using iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of an HDV gene for inhibiting the expression of an HDV gene. As HDV depends on obligatory helper functions provided by HBV for transmission, the methods for treatment of HDV can comprise agents and therapies useful for treating an HBV infection and/or an HBV-associated disorder, such as hepatitis D virus infection, chronic hepatitis D infection (CHD), chronic Hepatitis B infection (CHB), cirrhosis, liver failure, and hepatocellular carcinoma (HCC).

In certain examples, the RNAi agents as described herein have been designed to target regions in the HDV genomes that are conserved across at least two, preferably 3, or more of the 8 serotypes of HDV (HDV-1, HDV-2, HDV-3, HDV-4, HDV-5, HDV-6, HDV-7, and HDV-8).

Accordingly, in one example, described herein aredouble stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:31, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:32, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:33, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:34, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:35, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:36, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:37, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:38, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In yet another example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:39, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:40, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:41, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:42, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:43, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:44, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2551, and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 2552, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker. In certain examples, the sense strand of the double stranded RNAi agents comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from nucleotides 1451-1484, nucleotides 1455-1480, nucleotides 1455-1474, or nucleotides 1417-1443 of the nucleotide sequence of SEQ ID NO:2551.

In one example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the antisense strand.

In another example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the sense strand.

In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one example, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sequences listed in any one of Tables 11, 12, 31, and 32.

In some examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequences of the sense strand and the antisense strand sequences of any one of duplexes AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, and AD-70275.1. In other examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequences of the sense strand and the antisense strand sequences of any one of duplexes AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, and AD-70295.1.

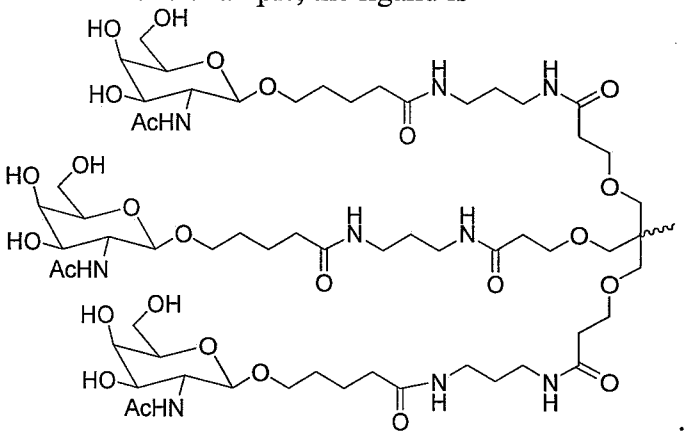
In one example, the at least one of the modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In one example, the at least one strand comprises a 3' overhang of at least 1 nucleotide. In another example, the at least one strand comprises a 3' overhang of at least 2 nucleotides.

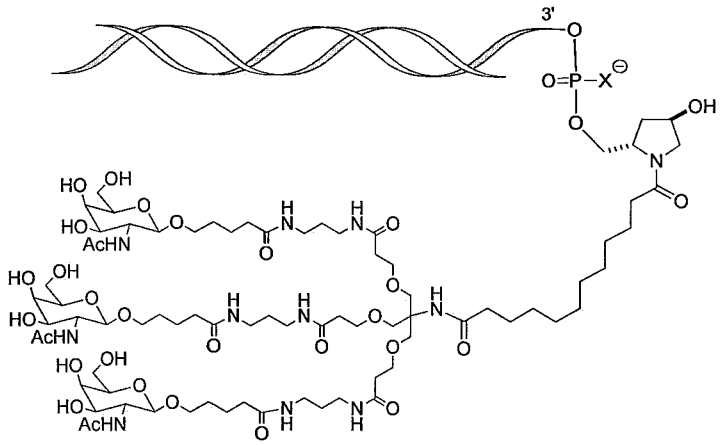
In one example, the double-stranded region is 15-30 nucleotide pairs in length. In another example, the double-stranded region is 17-23 nucleotide pairs in length. In yet another example, the double-stranded region is 17-25 nucleotide pairs in length. In one example, the e double-stranded region is 23-27 nucleotide pairs in length. In another example, the double-stranded region is 19-21 nucleotide pairs in length. In yet another example, the double-stranded region is 21-23 nucleotide pairs in length.

In one example, each strand has 15-30 nucleotides. In another example, each strand has 19-30 nucleotides.

In one example, the ligand is



In one example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one example, the RNAi agent is selected from the group of RNAi agents listed in any one of Tables 11, 12, 31, and 32.

In one example the agent is selected from the group consisting of AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-

67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, and AD-70275.1.

In one example, described herein are double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell. The double stranded RNAi agents include a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises any one of the sense sequences from Tables 11, 12, 31, and 32, and the antisense strand comprises any one of the antisense sequences from Tables 11, 12, 31, and 32, wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides, wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, the sense strand is selected from the group consisting of the sense strand sequences of AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1.

In another example, the antisense strand is selected from the group consisting of the antisense strand sequences of AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1.

The present disclosure also provides RNAi agents comprising sense and antisense nucleotide sequences which are at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over their entire length to the foregoing sense and antisense nucleotide sequences

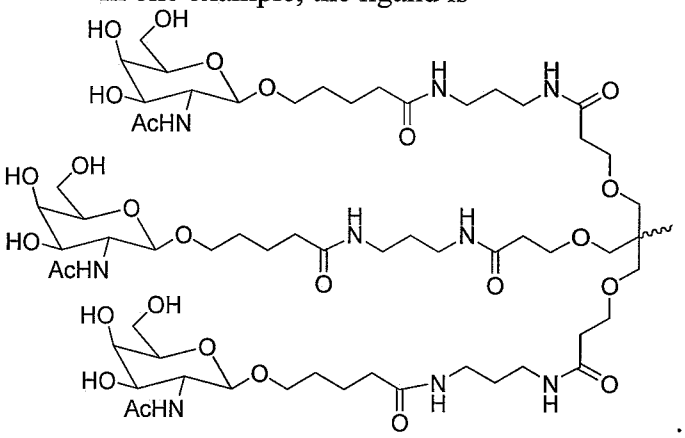
In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

In one example, at least one of the modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide,

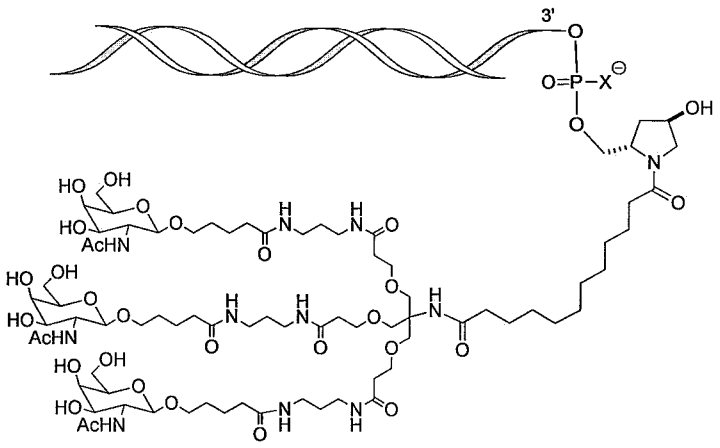
a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In one example, the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

In one example, the ligand is



In one example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:29, and each of the antisense strands independently comprises at least 15 contiguous nucleotides

differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:30, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:31, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:32, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:33, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:34, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the

ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In yet another example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:35, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:36, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:37, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:38, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID

NO:39, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:40, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:41, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:42, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:43, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:44, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In another example, described herein are compositions comprising two or more double stranded RNAi agents for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein each double stranded RNAi agent independently comprises a sense strand and an antisense strand forming a double-stranded region, wherein each of the sense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2551, and each of the antisense strands independently comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:2552, wherein substantially all of the nucleotides of each of the sense strands and substantially all of the nucleotides of each of the antisense strands are independently modified nucleotides, wherein each of the sense strands are independently conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In certain examples, the sense strand of one or both of the first and second double stranded RNAi agents comprises at least 15 contiguous nucleotides from nucleotides 1451-1484, nucleotides 1455-1480, nucleotides 1455-1474, or nucleotides 1417-1443 of the nucleotide sequence of SEQ ID NO:2551.

In one example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the antisense strand. In another example, the one or more of the 3 nucleotide differences in the nucleotide sequence of the antisense strand is a nucleotide mismatch in the sense strand.

In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one example, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sequences listed in any one of Tables 11, 12, 31, and 32.

In some examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequences of the sense strand and the antisense strand sequences of any one of duplexes AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-

67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1.

In other examples, the sense strand and the antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequences of the sense strand and antisense strand sequences of any one of duplexes AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, or AD-70295.1.

In one example, the at least one of the modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In another example, described herein are compositions for inhibiting expression of hepatitis D virus (HDV) in a cell, the composition comprising (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides, wherein the first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the second sense strand and substantially all of the nucleotides of the second antisense strand are modified nucleotides, wherein the second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first and second sense strands each independently comprise a sequence

selected from the group consisting of any one of the sense sequences from Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences), and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of any one of the antisense sequences from Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In one example, the first and second sense strands each independently comprise a sequence selected from the group consisting of any one of the sense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In another example, the first and second antisense strands each independently comprise a sequence selected from the group consisting of any one of the antisense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In one example, the first and second sense strand and/or all of the nucleotides of the first and second antisense strand comprise a modification.

In one example, the at least one of the modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base

comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In one example, the first and second RNAi agent are selected from the group consisting of any one of the the sequences provided in Tables 11, 12, 31, and 32.

In one example, the first and second RNAi agent are selected from the group consisting of any one of AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1.

In one example, the first and second RNAi agent are selected from the group consisting of any one of AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, or AD-70295.1.

In one example, described herein are a double stranded RNAi agent comprising any one of the RNAi agents listed in any one of Tables 11, 12, 31, 32,

In one example the agent is selected from the group consisting of AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1. In another example, the agent is selected from the group consisting of AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, or AD-70295.1.

The present disclosure also provides vectors and cells comprising the double stranded RNAi agent described herein are.

In another example, described herein are pharmaceutical compositions comprising the double stranded RNAi agents described herein are, or the compositions described herein are, or the vectors described herein are.

In one example, the double stranded RNAi agent is administered in an unbuffered solution. In one example, the unbuffered solution is saline or water.

In another example, the double stranded RNAi agent is administered with a buffer solution. In one example, the buffer solution comprises acetate, citrate,

prolamine, carbonate, or phosphate or any combination thereof. In another example, the buffer solution is phosphate buffered saline (PBS).

In one example, described herein are methods of inhibiting Hepatitis D virus (HDV) gene expression in a cell. The methods include contacting the cell with the double stranded RNAi agent described herein are, or the composition described herein are, or the vector described herein are, or the pharmaceutical composition described herein are; and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of an HDV gene, thereby inhibiting expression of the HDV gene in the cell.

In one example, described herein are methods of inhibiting replication of a Hepatitis D virus (HDV) in a cell. The methods include contacting the cell with the double stranded RNAi agent described herein are, or the composition described herein are, or the vector described herein are, or the pharmaceutical composition described herein are; and maintaining the cell produced for a time sufficient to obtain degradation of the mRNA transcript of an HDV gene, thereby inhibiting replication of the HDV in the cell.

In one example, the cell is within a subject. In one example, the subject is a human.

In one example, the subject suffers from an HDV-associated disease.

In one example, HDV gene expression is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.

In one example, replication of HDV in the cell is inhibited by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or about 100%.

In one example, described herein are methods of reducing the level of Hepatitis D virus (HDV) DNA in a subject infected with HDV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent as described herein, or the composition as described herein, or the vector as described herein, or the pharmaceutical composition as described herein, thereby reducing the level of HDV DNA in the subject.

In another example, described herein are methods of reducing the level of a Hepatitis D virus (HDV) antigen in a subject infected with HDV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent as described herein, or the composition as described herein, or the vector as described herein, or the pharmaceutical composition as described herein, thereby reducing the level of the HDV antigen in the subject. The level of the large HDV

antigen may be reduced, the level of the small HDV antigen may be reduced, or the level of both the large and the small HDV antigens may be reduced.

In another example, described herein are methods of reducing the viral load of Hepatitis D virus (HDV) in a subject infected with HDV. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent as described herein, or the composition as described herein, or the vector as described herein, or the pharmaceutical composition as described herein, thereby reducing the viral load of HDV in the subject.

In one example, described herein are methods of treating a subject having a Hepatitis D virus (HDV) infection. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent as described herein, or the composition as described herein, or the vector as described herein, or the pharmaceutical composition as described herein, thereby treating the subject.

In another example, described herein are methods of treating a subject having a Hepatitis D virus (HDV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of the double stranded RNAi agent as described herein, or the composition as described herein, or the vector as described herein, or the pharmaceutical composition as described herein, thereby treating the subject.

In one example, the HDV-associated disorder is selected from the group consisting of hepatitis B virus infection, acute hepatits B, acute hepatitis D; acute fulminant hepatitis D; chronic hepatitis D; liver fibrosis; end-stage liver disease; hepatocellular carcinoma.

In one example, described herein are methods of treating a subject having a Hepatitis D virus (HDV) infection. The methods include administering to the subject a therapeutically effective amount of a double stranded RNAi agent, wherein the double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein the sense strand comprises any one sense sequences from any one of Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), and the antisense strand comprises any one of the antisense sequences from any one of Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequence), wherein substantially all of the nucleotides of the sense strand and substantially all of the nucleotides of the antisense strand are modified nucleotides,

wherein the sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker, thereby treating the subject.

In one example, the sense strand comprises a sequence selected from the group consisting of any one of the sense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

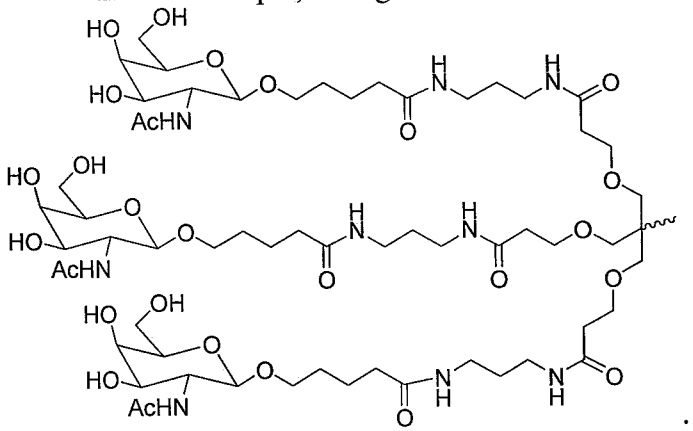
In another example, the antisense strand comprises a sequence selected from the group consisting of any one of the antisense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In one example, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand comprise a modification.

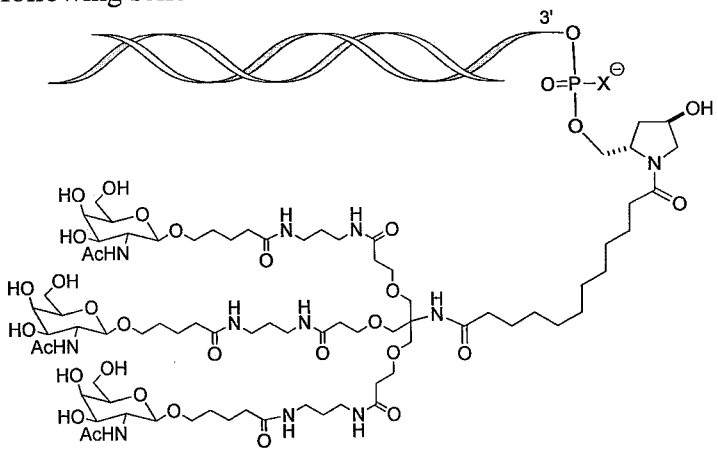
In one example, the at least one of the modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In one example, the 5'-phosphate mimic is a 5'-vinyl phosphate (5'-VP).

In one example, the ligand is



In one example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one example, the HDV-associated disorder is selected from the group consisting of hepatitis B virus infection, acute hepatits B, acute hepatitis D; acute fulminant hepatitis D; chronic hepatitis D; liver fibrosis; end-stage liver disease; hepatocellular carcinoma.

In one example, described herein are methods of treating a subject having a Hepatitis D virus (HDV) infection. The methods include administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis D virus (HDV) in a cell. The composition includes: (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides, wherein the first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc

derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the second sense strand and substantially all of the nucleotides of the second antisense strand are modified nucleotides, wherein the second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of any one of the sense sequences in any one of Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of any one of the antisense sequences from any one of Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), thereby treating the subject.

In one example, the first and second sense strands each independently comprise a sequence selected from the group consisting of any one of the sense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In another example, the first and second antisense strands each independently comprise a sequence selected from the group consisting of any one of the antisense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In another example, described herein are methods of treating a subject having a Hepatitis D virus (HDV)-associated disorder. The methods include administering to the subject a therapeutically effective amount of a composition for inhibiting expression of hepatitis D virus (HDV) in a cell. The composition includes: (a) a first double-stranded RNAi agent comprising a first sense strand and a first antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the first sense strand and substantially all of the nucleotides of the first antisense strand are modified nucleotides, wherein the first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and (b) a second double-stranded RNAi agent comprising a second sense strand and a second antisense strand forming a double-stranded region, wherein substantially all of the nucleotides of the second sense strand and substantially all of the nucleotides of the second antisense strand are modified nucleotides, wherein the second sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; wherein the first and second sense strands each independently comprise a sequence selected from the group consisting of any one of the sense sequences from any one of Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), and wherein the first and second antisense strands each independently comprise a sequence selected from the group consisting of any one of the antisense sequences from any one of Tables 11, 12, 31, and 32 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to any of the foregoing nucleotide sequences), thereby treating the subject.

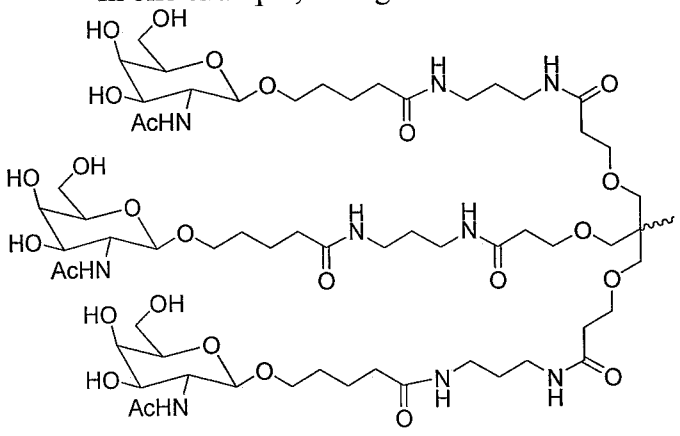
In one example, the first and second sense strands each independently comprise a sequence selected from the group consisting of any one of the sense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In another example, the first and second antisense strands each independently comprise a sequence selected from the group consisting of any one of the antisense sequences from AD-70260.1, AD-70232.1, AD-70249.1, AD-70244.1, AD-70272.1, AD-70228.1, AD-70255.1, AD-70278.1, AD-70295.1, AD-67200.1, AD-67211.1, AD-67199.1, AD-67202.1, AD-67208.1, AD-67210.1, AD-70259.1, AD-70267.1, AD-70272.1, AD-70271.1, AD-70268.1, AD-70269.1, AD-70232.1, AD-70256.1, AD-70257.1, or AD-70275.1 (or a nucleotide sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical over its entire length to the foregoing nucleotide sequences).

In one example, all of the nucleotides of the first and second sense strand and all of the nucleotides of the first and second antisense strand comprise a modification.

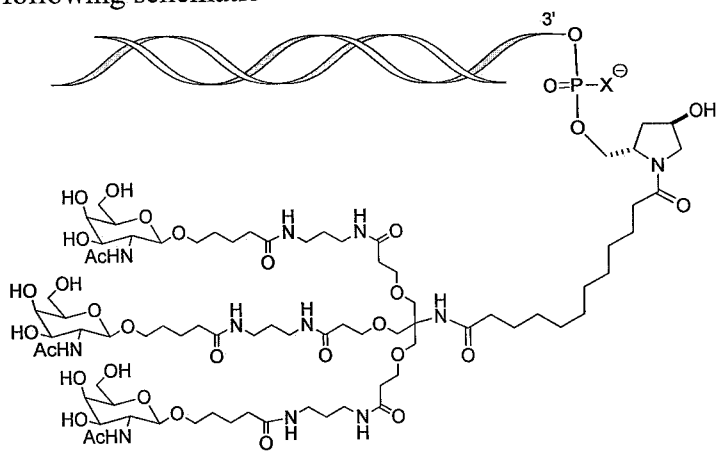
In one example, the at least one of the modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

In one example, the ligand is



.

In one example, the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

In one example, the subject is a human.

In one example, the HDV-associated disorder is selected from the group consisting of hepatitis B virus infection, acute hepatits B, acute hepatitis D; acute fulminant hepatitis D; chronic hepatitis D; liver fibrosis; end-stage liver disease; hepatocellular carcinoma.

In some examples, the methods as described herein further comprise treatment of hepatitis B virus (HBV) in the subject. Methods of treatment can include any methods of treatment known in the art. In certain examples, HBV is treated in the subject using one of more if the iRNA agents provided herein.

In some examples, the methods described herein are further include methods to modulate, preferably decrease the expression of PD-L1. Compositions and methods to reduce the expression of PD-L1 are provided, for example, in PCT publication no. WO2011/127180, which is hereby incorporated by reference.

In one example, the double stranded RNAi agent is administered at a dose of about 0.01 mg/kg to about 10 mg/kg or about 0.5 mg/kg to about 50 mg/kg.

In one example, the double stranded RNAi agent is administered at a dose of about 10 mg/kg to about 30 mg/kg. In another example, the double stranded RNAi agent is administered at a dose of about 3 mg/kg. In one example, the double stranded RNAi agent is administered at a dose of about 10 mg/kg.

In one example, the double stranded RNAi agent is administered at a dose of about 0.5 mg/kg twice per week.

In one example, the double stranded RNAi agent is administered at a fixed dose of about 50 mg to 200 mg.

In one example, the double stranded RNAi agent is administered subcutaneously. In another example, the double stranded RNAi agent is administered intravenously. In another example, the agent is administered intramuscularly.

In one example, the RNAi agent is administered in two or more doses.

In one example, the RNAi agent is administered at intervals selected from the group consisting of once every about 12 hours, once every about 24 hours, once every about 48 hours, once every about 72 hours, and once every about 96 hours.

In one example, the RNAi agent is administered twice per week. In another example, the RNAi agent is administered every other week.

In one example, the methods described herein are further include administering to the subject an additional therapeutic agent.

In one example, the additional therapeutic agent is selected from the group consisting of 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, a cccDNA inhibitor, a double-stranded iRNA agent targeting HBV, and a combination of any of the foregoing.

In another example, the methods described herein are further include administering administering to the subject a reverse transcriptase inhibitor. In yet another example, the methods described herein are further include administering to the subject a reverse transcriptase inhibitor and an immune stimulator.

In one example, the reverse transcriptase inhibitor is slected from the group consisting of Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, and AGX-1009.

In one example, the immune stimulator is selected from the group consisting of pegylated interferon alfa 2a (PEG-IFN-α2a), Interferon alfa-2b, a recombinant human interleukin-7, and aToll-like receptor 7 (TLR7) agonist.

In one example, the double-stranded iRNA agent targeting HBV is any one of the agents provided in any one of Tables 3, 4, 6, 14, 15, 24, 25, 27, and 28. In another example, the agent is AD-65403, AD-66810, or a combination thereof.

Detailed Description of the Invention

The present invention provides iRNA compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a Hepatitis D virus (HDV) gene. The gene may be within a cell, *e.g.*, a cell within a

We claim:

1. A double stranded RNAi agent for inhibiting expression of hepatitis D virus (HDV) in a cell, wherein said double stranded RNAi agent comprises a sense strand and an antisense strand forming a double-stranded region, wherein said sense strand and said antisense strand comprise a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the sense and antisense strands of SEQ ID NO: 1963, SEQ ID NO: 2141, SEQ ID NO: 1935, SEQ ID NO: 2113, SEQ ID NO: 1952, SEQ ID NO: 2130, SEQ ID NO: 1947, SEQ ID NO: 2125, SEQ ID NO: 1975, SEQ ID NO: 2153, SEQ ID NO: 1931, SEQ ID NO: 2109, SEQ ID NO: 1958, SEQ ID NO: 2136, SEQ ID NO: 1981, SEQ ID NO: 2159, SEQ ID NO: 1998, SEQ ID NO: 2176, SEQ ID NO: 1863, SEQ ID NO: 2041, SEQ ID NO: 1874, SEQ ID NO: 2052, SEQ ID NO: 1862, SEQ ID NO: 2040, SEQ ID NO: 1865, SEQ ID NO: 2043, SEQ ID NO: 1871, SEQ ID NO: 2049, SEQ ID NO: 1873, SEQ ID NO: 2051, SEQ ID NO: 1962, SEQ ID NO: 2140, SEQ ID NO: 1970, SEQ ID NO: 2148, SEQ ID NO: 1974, SEQ ID NO: 2152, SEQ ID NO: 1971, SEQ ID NO: 2149, SEQ ID NO: 1972, SEQ ID NO: 2150, SEQ ID NO: 1959, SEQ ID NO: 2137, SEQ ID NO: 1960, SEQ ID NO: 2138, SEQ ID NO: 1978, and SEQ ID NO: 2156.

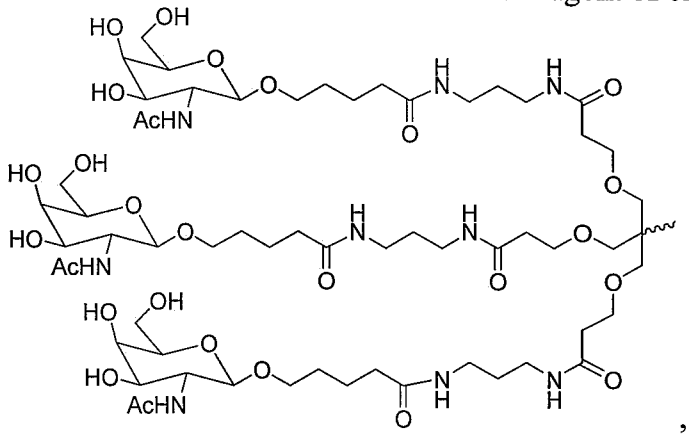
2. The double stranded RNAi agent of claim 1, wherein at least one of said modified nucleotides is selected from the group consisting of a 3'-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally restricted nucleotide, a constrained ethyl nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxly-modified nucleotide, a 2'-methoxyethyl modified nucleotide, a 2'-O-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, a tetrahydropyran modified nucleotide, a 1,5-anhydrohexitol modified nucleotide, a cyclohexenyl modified nucleotide, a nucleotide comprising a phosphorothioate group, a nucleotide comprising a methylphosphonate group, a nucleotide comprising a 5'-phosphate, and a nucleotide comprising a 5'-phosphate mimic.

3. The double stranded RNAi agent of claim 1, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide or at least one strand comprises a 3' overhang of at least 2 nucleotides.

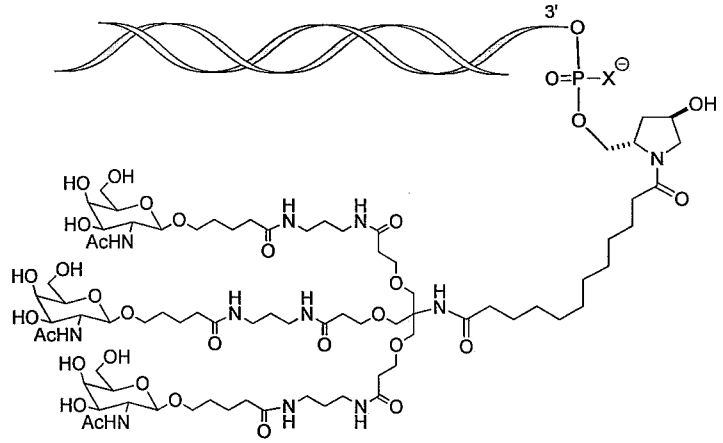
4. The double stranded RNAi agent of claim 1, wherein the double-stranded region is 15-30 nucleotide pairs in length; 17-23 nucleotide pairs in length; 17-25 nucleotide pairs in length; 23-27 nucleotide pairs in length; 19-21 nucleotide pairs in length; 21-23 nucleotide pairs in length.

5. The double stranded RNAi agent of claim 1, wherein each strand has 15-30 nucleotides.

6. The double stranded RNAi agent of claim 1, wherein the ligand is



, optionally, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

7. The double stranded RNAi agent of claim 1, wherein said RNAi agent is a duplex comprising a sense strand and an antisense strand selected from the group ofpaired sense and antisense strands selected from SEQ ID NO: 1963 and SEQ ID NO: 2141; SEQ ID NO: 1935 and SEQ ID NO: 2113; SEQ ID NO: 1952 and SEQ ID NO: 2130; SEQ ID NO: 1947 and SEQ ID NO: 2125, SEQ ID NO: 1975 and SEQ ID NO: 2153; SEQ ID NO: 1931 and SEQ ID NO: 2109; SEQ ID NO: 1958 and SEQ ID NO: 2136; SEQ ID NO: 1981 and SEQ ID NO: 2159; SEQ ID NO: 1998 and SEQ ID NO: 2176; SEQ ID NO: 1863 and SEQ ID NO: 2041; SEQ ID NO: 1874 and SEQ ID NO: 2052; SEQ ID NO: 1862 and SEQ ID

NO: 2040; SEQ ID NO: 1865 and SEQ ID NO: 2043; SEQ ID NO: 1871 and SEQ ID NO: 2049; SEQ ID NO: 1873 and SEQ ID NO: 2051; SEQ ID NO: 1962 and SEQ ID NO: 2140; SEQ ID NO: 1970 and SEQ ID NO: 2148; SEQ ID NO: 1974 and SEQ ID NO: 2152; SEQ ID NO: 1971 and SEQ ID NO: 2149; SEQ ID NO: 1972 and SEQ ID NO: 2150; SEQ ID NO: 1959 and SEQ ID NO: 2137; SEQ ID NO: 1960 and SEQ ID NO: 2138; SEQ ID NO: 1978 and SEQ ID NO: 2156; SEQ ID NO: 2319 and SEQ ID NO: 2497; SEQ ID NO: 2291 and SEQ ID NO: 2469; SEQ ID NO: 2308 and SEQ ID NO: 2486; SEQ ID NO: 2303 and SEQ ID NO: 2481; SEQ ID NO: 2331 and SEQ ID NO: 2509; SEQ ID NO: 2287 and SEQ ID NO: 2465; SEQ ID NO: 2314 and SEQ ID NO: 2492; SEQ ID NO: 2337 and SEQ ID NO: 2515; SEQ ID NO: 2354 and SEQ ID NO: 2532; SEQ ID NO: 2219 and SEQ ID NO: 2397; SEQ ID NO: 2230 and SEQ ID NO: 2408; SEQ ID NO: 2218 and SEQ ID NO: 2396; SEQ ID NO: 2221 and SEQ ID NO: 2399; SEQ ID NO: 2227 and SEQ ID NO: 2405; SEQ ID NO: 2229 and SEQ ID NO: 2407; SEQ ID NO: 2318 and SEQ ID NO: 2496; SEQ ID NO: 2326 and SEQ ID NO: 2504; SEQ ID NO: 2331 and SEQ ID NO: 2509; SEQ ID NO: 2330 and SEQ ID NO: 2508; SEQ ID NO: 2327 and SEQ ID NO: 2505; SEQ ID NO: 2328 and SEQ ID NO: 2506; SEQ ID NO: 2315 and SEQ ID NO: 2493; SEQ ID NO: 2316 and SEQ ID NO: 2494; and SEQ ID NO: 2334 and SEQ ID NO: 2512.

8. A composition comprising two or more double stranded RNAi agents of any one of claims 1-7 for inhibiting expression of hepatitis D virus (HDV) in a cell.

9. A composition for inhibiting expression of hepatitis D virus (HDV) in a cell, said composition comprising:

(a) a first double-stranded RNAi agent comprising an RNAi agent according to claim 7,

wherein not more than 5, 4, 3, 2, or 1 of the nucleotides of said first sense strand and not more than 5, 4, 3, 2, or 1 of the nucleotides of said first antisense strand are unmodified nucleotides,

wherein said first sense strand is conjugated to a ligand attached at the 3'-terminus, and wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker; and

(b) a second double-stranded RNAi agent comprising an RNAi agent according to claim 7,

wherein not more than 5, 4, 3, 2, or 1 of the nucleotides of said second sense strand and not more than 5, 4, 3, 2, or 1 of the nucleotides of said second antisense strand are unmodified nucleotides,

wherein said second sense strand is conjugated to a ligand attached at the 3'-terminus, and

wherein the ligand is one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

10. A pharmaceutical composition comprising the double stranded RNAi agent of claim 1 or 7, or the composition of claim 8 or 9.

11. An *in vitro* method of inhibiting Hepatitis D virus (HDV) gene expression or replication in a cell, the method comprising:

(a) contacting the cell with the double stranded RNAi agent of claim 1 or 7, the composition of claim 8 or 9; and

(b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of an HDV gene, thereby inhibiting expression or replication of the HDV gene in the cell.

12. Use of the double stranded RNAi agent of claim 1 or 7, or the composition of claim 8 or 9, or the pharmaceutical composition of claim 10 in the manufacture of a medicament for treating a subject having a Hepatitis D virus (HDV) infection.

13. The use of claim 12, wherein the double stranded RNAi agent is to be administered at a dose of 0.01 mg/kg to 10 mg/kg; 0.5 mg/kg to 50 mg/kg; 10 mg/kg to 30 mg/kg; 3 mg/kg; 10 mg/kg; or at a fixed dose of 50 mg to 200 mg.

14. The use of claim 12, wherein the double stranded RNAi agent is to be administered subcutaneously or intravenously.

15. The use of claim 12, further comprising an additional therapeutic agent, optionally an antiviral agent, a reverse transcriptase inhibitor (e.g., Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide, Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, or AGX-1009), 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), a therapeutic vaccine, a viral entry inhibitor, an oligonucleotide that inhibits the secretion or release of HbsAg, a capsid inhibitor, a covalently closed circular (ccc) HBV DNA inhibitor, a double-stranded iRNA agent targeting HBV e.g., a double-stranded iRNA agent targeting HBV is any one of the agents provided in any one of Tables 3, 4, 6, 14, 15, 24, 25, 27, and 28, e.g., AD-65403, AD-66810, or a combination thereof), and a combination of any of the foregoing.