SUMMARY

In one aspect, the present disclosure refers to the use of an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load and an anti-HBV antibody in the manufacture of a medicament for combination therapy to treat a chronic hepatitis B virus (HBV) infection or a HBV-associated disease in a subject, wherein: (a) the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively; and (b) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA that inhibits expression of an HBV transcript, the siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein: (i) 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; (ii) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (iii) (Agn) is adenosine-glycol nucleic acid (GNA); (iv) s is a phosphorothioate linkage; and (v) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol. In another aspect, the present disclosure refers to the use of an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a first medicament and use of an anti-HBV antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a chronic hepatitis B virus (HBV) infection or a HBV-associated disease in a subject, wherein: (a) the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively; and (b) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA that inhibits expression of an HBV transcript, the siRNA having a sense strand

comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:(i) 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; (ii) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (iii) (Agn) is adenosine-glycol nucleic acid (GNA); (iv) s is a phosphorothioate linkage; and (v) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol. In another aspect, the present disclosure refers to the use of an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a medicament for use in combinatorial therapy for treating a chronic hepatitis B virus (HBV) infection or a HBV-associated disease in a subject, wherein said medicament is to be administered in combination with an anti-HBV antibody, wherein: (a) the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively; and (b) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA that inhibits expression of an HBV transcript, the siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein: (i) 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; (ii) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (iii) (Agn) is adenosine-glycol nucleic acid (GNA); (iv) s is a phosphorothioate linkage; and (v) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol. In some examples, the present disclosure provides an inhibitor of HBV gene expression for use in the treatment of a chronic HBV infection in a subject, wherein the subject is subsequently administered an anti-HBV antibody.

The present disclosure also provides an agent that reduces HBV antigenic load for use in the treatment of a chronic HBV infection in a subject, wherein the subject is subsequently administered an anti-HBV antibody.

The present disclosure also provides a composition for use in the treatment of a chronic HBV infection in a subject, wherein (a) the composition comprises an anti-HBV antibody and the subject has been previously administered an inhibitor of gene expression; or (b) composition comprises an anti-HBV antibody and the subject has been previously administered an agent that reduces HBV antigenic load.

In another aspect, the present disclosure refers to the use of (a) an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load and (b) an anti-HBV antibody, in the manufacture of a medicament for combination therapy to treat a chronic HBV infection or a HBV-associated disease in a subject, wherein: (1) the anti-HBV antibody comprises a light chain amino acid sequence according to SEQ ID NO:73, and a heavy chain amino acid sequence according to SEQ ID NO:71; and (2) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein: (a) 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; (b) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (c) (Agn) is adenosine-glycol nucleic acid (GNA); (d) s is a phosphorothioate linkage; and (e) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol. In another aspect, the present disclosure refers to the use of (a) an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a first medicament and use of (b) an anti-HBV antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a chronic HBV infection or a HBV-associated disease in a subject, wherein: (1) the anti-HBV antibody comprises a light chain amino acid sequence according to SEQ ID NO:73, and a heavy chain amino acid sequence according to SEQ ID

NO:71; and (2) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein: (a) 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; (b) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (c) (Agn) is adenosine-glycol nucleic acid (GNA); (d) s is a phosphorothioate linkage; and (e) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

In another aspect, the present disclosure refers to the use of (a) an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a medicament for use in combinatorial therapy for treating a chronic HBV infection or a HBV-associated disease in a subject, wherein said medicament is to be administered in combination with (b) an anti-HBV antibody, wherein: (1) the anti-HBV antibody comprises a light chain amino acid sequence according to SEQ ID NO:73, and a heavy chain amino acid sequence according to SEQ ID NO:71; and (2) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA having a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein: (a) 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; (b) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (c) (Agn) is adenosine-glycol nucleic acid (GNA); (d) s is a phosphorothioate linkage; and (e) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

In some examples, the present disclosure provides for the use of an inhibitor of HBV gene expression and an anti-HBV antibody in the manufacture of a medicament for the treatment of a chronic HBV infection. The present disclosure also provides for the use

of agent that reduces HBV antigenic load and an anti-HBV antibody in the manufacture of a medicament for the treatment of a chronic HBV infection.

In some examples, the present disclosure provides a method of treating chronic HBV infection in a subject in need thereof, comprising: administering to the subject an agent that reduces HBV antigenic load; and administering to the subject an anti-HBV antibody. The present disclosure also provides a method of treating chronic HBV infection in a subject in need thereof, comprising: administering to the subject an inhibitor of HBV gene expression; and administering to the subject an anti-HBV antibody.

In some methods, compositions for use, or uses described herein, the anti-HBV antibody is HBC34 or a non-natural variant of HBC34.

In some methods, compositions for use, or uses described herein, the agent that reduces HBV antigenic load or the inhibitor of HBV gene expression is an RNAi agent (*e.g.*, an siRNA, such as HBV02).The present disclosure also provides, in some examples, kits comprising an RNAi agent and an anti-HBV antibody as disclosed herein, optionally with instructions for practicing a method described herein. In yet another aspect, the present disclosure refers to a kit comprising: (1) a pharmaceutical composition comprising an RNAi agent that targets an mRNA encoded by an HBV gene, and a pharmaceutically acceptable excipient, wherein the RNAi agent is an siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein: (i) 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;
(ii) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively; (iii) (Agn) is adenosine-glycol nucleic acid (GNA); (iv) s is a phosphorothioate linkage; and (v) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol89rt; and (2) a pharmaceutical composition comprising an anti-HBV antibody, and a pharmaceutically acceptable excipient, wherein the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively.

CLAIMS

That which is claimed is:

1. Use of an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load and an anti-HBV antibody in the manufacture of a medicament for combination therapy to treat a chronic hepatitis B virus (HBV) infection or a HBV-associated disease in a subject, wherein:

(a) the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively; and

(b) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA that inhibits expression of an HBV transcript, the siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3**'** (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:

(i) 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;

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

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

(iv) s is a phosphorothioate linkage; and

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

2. Use of an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a first medicament and use of an anti-HBV antibody in the manufacture of a second medicament, wherein the first and second

medicaments are to be used in combination therapy to treat a chronic hepatitis B virus (HBV) infection or a HBV-associated disease in a subject, wherein:

(a) the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively; and

(b) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA that inhibits expression of an HBV transcript, the siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:

(i) 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;

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

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

(iv) s is a phosphorothioate linkage; and

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

3. Use of an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a medicament for use in combinatorial therapy for treating a chronic hepatitis B virus (HBV) infection or a HBV-associated disease in a subject, wherein said medicament is to be administered in combination with an anti-HBV antibody, wherein:

(a) the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively; and

(b) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA that inhibits expression of an HBV transcript, the siRNA having a sense strand comprising 5'- gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:

(i) 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;

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

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

(iv) s is a phosphorothioate linkage; and

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

4. The use according to any one of claims 1 to 3, wherein (a) a therapeutically effective amount of the anti-HBV antibody is less than a therapeutically effective amount of the anti-HBV antibody delivered when the inhibitor of HBV gene expression or the agent that reduces HBV antigenic load has not been administered to the subject; or (b) the anti-HBV antibody is to be administered at least 1 week after the inhibitor of HBV gene expression or the agent that reduces HBV antigenic load has been administered.

5. The use according to any one of the preceding claims, wherein at least two doses of a therapeutically effective amount of the anti-HBV antibody is to be administered.

6. The use according to claim 5, wherein the at least two doses are to be administered twice per week, once per week, every other week, every two weeks, or once a month.

7. The use according to any one of the preceding claims, wherein the anti-HBV antibody is to be administered subcutaneously.

8. The use according to any one of the preceding claims, wherein the anti-HBV antibody comprises:

(a) a light chain variable domain (V_L) that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in any one of SEQ ID NOs:55-69; and (b) a heavy chain variable domain (V_H) that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:53: or

(a) a light chain variable domain (V_L) that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in any one of SEQ ID NOs:55-69; and (b) a heavy chain variable domain (V_H) that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:54.

9. The use according to any one of the preceding claims, wherein the anti-HBV antibody comprises:

(a) a light chain variable domain (V_L) amino acid sequence according to SEQ ID NO:59; and (b) a heavy chain variable domain (V_H) amino acid sequence according to SEQ ID NO:53.

10. The use according to any one of the preceding claims, wherein the anti-HBV antibody comprises:

(a) a light chain that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:73, and (b) a heavy chain that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in any one of SEQ ID NOs:70-72 and 97; or

(a) a light chain that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:74, and (b) a heavy chain that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in any one of SEQ ID NOs:70-72 and 97; or

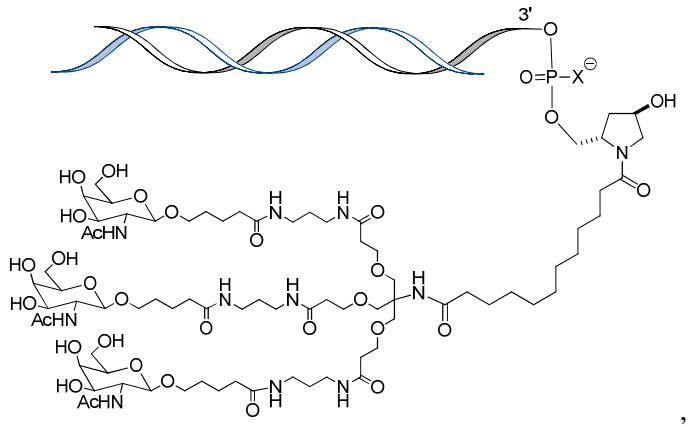
(a) a light chain that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in SEQ ID NOs:83-95, and (b) a heavy chain that is at least 90%, at least 95%, or 100% identical to the amino acid sequence set forth in any one of SEQ ID NOs:70-72, 97, and 98.

11. The use according to any one of the preceding claims, wherein the anti-HBV antibody comprises:

(i) a light chain variable domain (VL) amino acid sequence according to SEQ ID NO:73; and (ii) a heavy chain variable domain (VH) amino acid sequence according to SEQ ID NO:71.

12. The use according to any one of the preceding claims, wherein the subject is a human and a therapeutically effective amount of the anti-HBV antibody is to be administered; wherein the therapeutically effective amount is from 3 mg/kg to 30 mg/kg.

13. The use according to any one of the preceding claims, wherein the siRNA is conjugated to the L96 as shown in the following structure:



,

wherein X is O.

14. The use according to any one of the preceding claims, wherein (a) the subject is a human and a therapeutically effective amount of RNAi agent or siRNA is to be administered to the subject; and wherein the effective amount of the RNAi agent or siRNA is from 1 mg/kg to 8 mg/kg; or (b) the RNAi agent or siRNA is to be administered to the subject twice daily, once daily, every two days, every three days, twice per week, once per week, every other week, every four weeks, or once per month.

15. The use according to any one of the preceding claims, wherein the subject is also to be administered a nucleot(s)ide analog.

16. Use of (a) an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load and (b) an anti-HBV antibody, in the manufacture of a medicament for combination therapy to treat a chronic HBV infection or a HBV-associated disease in a subject, wherein:

(1) the anti-HBV antibody comprises a light chain amino acid sequence according to SEQ ID NO:73, and a heavy chain amino acid sequence according to SEQ ID NO:71; and

(2) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA having a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:

(a) 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;

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

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

(d) s is a phosphorothioate linkage; and

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

17. Use of (a) an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a first medicament and use of (b) an anti-HBV antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a chronic HBV infection or a HBV-associated disease in a subject, wherein:

(1) the anti-HBV antibody comprises a light chain amino acid sequence according to SEQ ID NO:73, and a heavy chain amino acid sequence according to SEQ ID NO:71; and

(2) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA having a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3**'** (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:

(a) 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;

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

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

(d) s is a phosphorothioate linkage; and

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

18. Use of (a) an inhibitor of HBV gene expression or an agent that reduces HBV antigenic load in the manufacture of a medicament for use in combinatorial therapy for treating a chronic HBV infection or a HBV-associated disease in a subject, wherein said medicament is to be administered in combination with (b) an anti-HBV antibody, wherein:

(1) the anti-HBV antibody comprises a light chain amino acid sequence according to SEQ ID NO:73, and a heavy chain amino acid sequence according to SEQ ID NO:71; and

(2) the inhibitor of HBV gene expression or agent that reduces HBV antigenic load is an siRNA having a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:

(a) 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;

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

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

(d) s is a phosphorothioate linkage; and

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

19. The use of any one of claims 16 to 18, wherein the anti-HBV antibody is to be administered to the subject at least 1 week after the siRNA has been administered to the subject.

20. The use of any one of claims 16 to 19, wherein the subject is also to be administered a nucleot(s)ide analog.

21. The use according to any one of the preceding claims, wherein the HBV-associated disease is a hepatitis D virus (HDV) infection, delta hepatitis, acute hepatitis B; acute fulminant hepatitis B; chronic hepatitis B; liver fibrosis; end-stage liver disease; or hepatocellular carcinoma.

22. The use according to any one of the preceding claims, wherein the HBV-associated disease is a hepatitis D (HDV) infection.

23. The use according to any one of the preceding claims, wherein the subject has both a hepatitis B virus (HBV) infection and a hepatitis D virus (HDV) infection.

24. A kit comprising:

(1) a pharmaceutical composition comprising an RNAi agent that targets an mRNA encoded by an HBV gene, and a pharmaceutically acceptable excipient, wherein the RNAi agent is an siRNA having a sense strand comprising 5'-gsusguGfcAfCfUfucgcuucacaL96 -3' (SEQ ID NO:7) and an antisense strand comprising 5'- usGfsuga(Agn)gCfGfaaguGfcAfcacsusu -3' (SEQ ID NO:8), wherein:
(i) 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;
(ii) Af, Cf, Gf, and Uf are 2'-fluoroadenosine-3'-phosphate, 2'-fluorocytidine-3'-phosphate, 2'-fluoroguanosine-3'-phosphate, and 2'-fluorouridine-3'-phosphate, respectively;
(iii) (Agn) is adenosine-glycol nucleic acid (GNA);
(iv) s is a phosphorothioate linkage; and
(v) L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol89rt; and

(2) a pharmaceutical composition comprising an anti-HBV antibody, and a pharmaceutically acceptable excipient, wherein the anti-HBV antibody comprises (i) CDRH1, CDRH2, and CDRH3 amino acid sequences according to SEQ ID NOs:44, 45 or 46, and 47, respectively; and (ii) CDRL1, CDRL2, and CDRL3 amino acid sequences according to SEQ ID NOs:48, 49 or 50, and 52 or 51, respectively.