for long term storage making them less desirable for use in countries where HBV infection is most prevalent.

Treatment of chronic HBV is further complicated by the ability of HBV to evade or suppress the immune response resulting in persistence of the infection. The HBV proteins have immune-inhibitory properties, with hepatitis B s antigen (HBsAg) comprising the overwhelming majority of HBV protein in the circulation of HBV infected subjects. Additionally, while the removal (*via* seroconversion) of hepatitis B e antigen (HBeAg) or reductions in serum viremia are not correlated with the development of sustained control of HBV infection off treatment, the removal of serum HBsAg from the blood (and seroconversion) in HBV infection is a well-recognized prognostic indicator of antiviral response to treatment which will lead to control of HBV infection off treatment. However, this only occurs in a small fraction of patients receiving immunotherapy. Therefore, it is possible, although rare, for patients to mount a sufficiently robust immune response to suppress or clear an HBV infection resulting in at least a functional cure of the disease.

SUMMARY

The disclosure provides RNAi agents and HBV vaccines for use in treatment of hepatitis B virus (HBV) infection and methods for the treatment of a subject having a hepatitis B virus (HBV) infection, *e.g.,* a chronic HBV infection, which includes a combination therapy or treatment regimen including an RNAi agent targeting at least one HBV transcript and a therapeutic vaccination.

In one aspect, the present disclosure refers to the use of an RNAi agent in the manufacture of a first medicament, use of a protein-based HBV vaccine in the manufacture of a second medicament, and use of a nucleic acid-based HBV vaccine in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used for a conmbination therapy for treating a hepatitis B virus (HBV) infection, wherein: a) the RNAi agent inhibits expression of at least three HBV transcripts, and comprises a sense strand and an antisense strand forming a double stranded region, and (i) the sense strand comprises the nucleotide sequence of 5'-GUGUGCACUUCGCUUCACA-3' (SEQ ID NO: 27) and the antisense strand comprises the nucleotide sequence of 5'-UGUGAAGCGAAGUGCACACUU-3' (SEQ ID NO: 25), or (ii) the sense strand comprises the nucleotide sequence of 5'-CACCAUGCAACUUUUUCACCU-3' (SEQ ID NO: 28) and the antisense strand comprises the nucleotide sequence of 5'-AGGUGAAAAAGUUGCAUGGUGUU-3' (SEQ ID NO: 26); b) the protein-based HBV vaccine comprises a first HBV core antigen (HBcAg) polypeptide, or immunogenic fragment thereof, and a first HBV surface antigen (HBsAg) polypeptide, or immunogenic fragment thereof; c) the nucleic acid-based HBV vaccine comprising an expression vector construct encoding a second HBcAg polypeptide, or immunogenic fragment thereof, and/or a second HBsAg polypeptide, or immunogenic fragment thereof; d) the second HBcAg polypeptide, or immunogenic fragment thereof, and/or the second HBsAg polypeptide, or immunogenic fragment thereof, shares at least one epitope with at least one of the first HBcAg polypeptide, or immunogenic fragment thereof, and/or the first HBsAg polypeptide, or immunogenic fragment thereof; and (e) the RNAi agent, the protein-based HBV vaccine is to be administered to a subject having an HBV infection prior to the protein-based HBV vaccine that is to be administered to the subject, and and the nucleic acid-based HBV vaccine that is to be administered to the subject.

~~In another aspect, the present disclosure refers to a kit for treating a subject having an HBV infection, the kit comprising: a) an RNAi agent that inhibits expression of at least three HBV transcripts, wherein the RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, and (i) the sense strand comprises the nucleotide sequence of 5'-GUGUGCACUUCGCUUCACA-3' (SEQ ID NO: 27) and the antisense strand comprises the nucleotide sequence of 5'-UGUGAAGCGAAGUGCACACUU-3' (SEQ ID NO: 25), or (ii) the sense strand comprises the nucleotide sequence of 5'-CACCAUGCAACUUUUUCACCU-3' (SEQ ID NO: 28) and the antisense strand comprises the nucleotide sequence of 5'-AGGUGAAAAAGUUGCAUGGUGUU-3' (SEQ ID NO: 26); b) a protein-based vaccine comprising a first HBV core antigen (HBcAg) polypeptide, or immunogenic fragment thereof, and a first HBV surface antigen (HBsAg)~~

~~polypeptide, or immunogenic fragment thereof; and c) a nucleic acid-based vaccine comprising an expression vector construct encoding a second HBcAg polypeptide, or immunogenic fragment thereof, and/or a second HBsAg polypeptide, or immunogenic fragment thereof, wherein the second HBcAg polypeptide, or immunogenic fragment thereof, and/or the second HBsAg polypeptide, or immunogenic fragment thereof, shares at least one epitope with at least one of the first HBcAg polypeptide, or immunogenic fragment thereof, and/or the first HBsAg polypeptide, or immunogenic fragment thereof; and d) instructions for use according to the uses as described herein.~~

Accordingly, in one example, the present disclosure provides RNAi agents and HBV vaccines for use in treatment of hepatitis B virus (HBV) infection and methods for treating a subject having a hepatitis B virus (HBV) infection, *e.g.,* a chronic HBV infection. The methods include a regimen which includes administering, *e.g.,* sequentially administering, to the subject having the HBV infection, an RNAi agent that targets at least three HBV transcripts, wherein the RNAi agent comprises a sense strand and an antisense strand; a protein-based vaccine comprising an HBV core antigen (HBcAg) and an HBV surface antigen (HBsAg); and a nucleic acid-based vaccine comprising an expression construct encoding an HBcAg or an HBsAg, wherein the construct encodes a protein that shares an epitope with the protein-based vaccine, thereby treating the subject.

In another example, the present disclosure provides a regimen for treating a subject having a hepatitis B virus (HBV) infection, *e.g.,* a chronic HBV infection. The regimen includes the use of an RNAi agent that targets at least three HBV transcripts, wherein the RNAi agent comprises a sense strand and an antisense strand; a protein-based vaccine comprising an HBV core antigen (HBcAg) and an HBV surface antigen (HBsAg); and a nucleic acid-based vaccine comprising an expression construct encoding an HBcAg or an HBsAg, wherein the construct encodes a protein that shares an epitope with the protein-based vaccine.

In one example, the HBcAg protein, or immunogenic fragment thereof, shares an epitope with the HBV core antigen (HBcAg) polypeptide, or immunogenic fragment thereof, present in the protein-based vaccine and/or the HBsAg protein, or immunogenic fragment thereof, shares an epitope with the HBV surface antigen (HBsAg) polypeptide, or immunogenic fragment thereof, present in the protein-based vaccine.

In certain examples, the RNAi agent comprises at least one modified nucleotide.

In certain examples, the nucleic acid-based vaccine comprises an expression construct encoding an HBcAg and an HBsAg.

In certain examples, the RNAi agent targeting HBV is administered to the subject at least two times.

In certain examples, the RNAi agent targeting HBV administered to the subject decreases HBsAg in the serum of the subject by at least 0.5 log 10 IU/ml. In certain examples, the subject has at least a 0.5 log10 IU/ml decrease in HBsAg in serum prior to administration of the first dose of the protein based vaccine. In certain examples, the subject has at least a 1 log10 IU/ml decrease in HBsAg in serum prior to administration of the first dose of the protein based vaccine. In certain

We claim:

1. Use of an RNAi agent in the manufacture of a first medicament, use of a protein-based HBV vaccine in the manufacture of a second medicament, and use of a nucleic acid-based HBV vaccine in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used for a combination therapy for treating a hepatitis B virus (HBV) infection, wherein:

a) the RNAi agent inhibits expression of at least three HBV transcripts, and comprises a sense strand and an antisense strand forming a double stranded region, and (i) the sense strand comprises the nucleotide sequence of 5'-GUGUGCACUUCGCUUCACA-3' (SEQ ID NO: 27) and the antisense strand comprises the nucleotide sequence of 5'-UGUGAAGCGAAGUGCACACUU-3' (SEQ ID NO: 25), or (ii) the sense strand comprises the nucleotide sequence of 5'-CACCAUGCAACUUUUUCACCU-3' (SEQ ID NO: 28) and the antisense strand comprises the nucleotide sequence of 5'-AGGUGAAAAAGUUGCAUGGUGUU-3' (SEQ ID NO: 26);

b) the protein-based HBV vaccine comprises a first HBV core antigen (HBcAg) polypeptide, or immunogenic fragment thereof, and a first HBV surface antigen (HBsAg) polypeptide, or immunogenic fragment thereof;

c) the nucleic acid-based HBV vaccine comprising an expression vector construct encoding a second HBcAg polypeptide, or immunogenic fragment thereof, and/or a second HBsAg polypeptide, or immunogenic fragment thereof;

d) the second HBcAg polypeptide, or immunogenic fragment thereof, and/or the second HBsAg polypeptide, or immunogenic fragment thereof, shares at least one epitope with at least one of the first HBcAg polypeptide, or immunogenic fragment thereof, and/or the first HBsAg polypeptide, or immunogenic fragment thereof; and

(e) the RNAi agent is to be administered to a subject having an HBV infection prior to the protein-based HBV vaccine that is to be administered to the subject, and the protein-based HBV vaccine is to be administered to the subject prior to the nucleic acid-based HBV vaccine that is to be administered to the subject.

2. The use of claim 1, wherein the nucleic acid-based HBV vaccine comprises an expression vector construct encoding the second HBcAg polypeptide, or immunogenic fragment thereof, and the second HBsAg polypeptide, or immunogenic fragment thereof.

3. The use of any of claims 1-2, wherein (a) the RNAi agent is to be administered to the subject such that the level of HBsAg in the serum of the subject is decreased by at least 0.5 log 10 IU/ml; (b) the level of HBsAg in the serum of the subject is decreased by at least a 0.5 log10 IU/ml, at least a 1 log10 IU/ml, or at least a 2 log 10 IU/ml prior to administration of a first dose of the protein-based HBV vaccine; (c) the level of HBeAg in the serum of the subject is decreased by at least a 1 log 10 IU/ml prior to administration of a first dose of the protein-based HBV vaccine; (d) the level of

HBsAg in the serum of the subject is decreased by at least a 2 log 10 IU/ml and the level of HBeAg in the serum of the subject is decreased by at least a 1 log 10 IU/ml prior to administration of a first dose of the protein based vaccine; (e) the subject has a serum HBsAg level of 500 IU/ml or less, 200 IU/ml or less, or 100 IU/ml or less after administration of the RNAi agent and prior to administration of a first dose of the protein-based HBV vaccine; (f) the subject has a serum HBeAg level of 500 IU/ml or less, 200 IU/ml or less, or 100 IU/ml or less after administration of the RNAi agent and prior to administration of a first dose of the protein-based HBV vaccine; (g) the level of serum HBsAg in the subject is below 3000 IU/ml, 4000 IU/ml, or 5000 IU/ml prior to administration of the RNAi agent; (h) the level of serum HBsAg in the subject is decreased to below the level of detection using a clinical assay for at least six months after the end of the dose of the nucleic acid-based HBV vaccine; (i) the level of serum HBeAg in the subject is decreased to below the level of detection using a clinical assay for at least six months after the end of the dose of the nucleic acid-based HBV vaccine; (j) the level of serum HBeAg in the subject is decreased to below the level of detection using a clinical assay for at least six months after the end of the dose of the nucleic acid-based HBV vaccine; or (k) the level of serum HBsAg and HBeAg in the subject are decreased to below the level of detection using a clinical assay for at least six months after the end of the dose of the nucleic acid-based HBV vaccine.

4. The use of any of claims 1-3, wherein (a) at least two doses of the RNAi agent are to be administered to the subject; or (b) a dose of the RNAi agent is to be administered to the subject no more than once per week or no more than once every four weeks.

5. The use of any one of claims 1-4, wherein the RNAi agent is to be administered to the subject at a dose of 0.01 mg/kg to 10 mg/kg; 0.5 mg/kg to 50 mg/kg; 10 mg/kg to 30 mg/kg; 0.5 mg/kg; 1 mg/kg; 1.5 mg/kg; 3 mg/kg; 5 mg/kg; 10 mg/kg; or 30 mg/kg.

6. The use of any of claims 1-5, wherein the first HBcAg polypeptide, or immunogenic fragment thereof, comprises at least one HBcAg determinant and the first HBsAg polypeptide, or immunogenic fragment thereof, comprises at least one HBsAg determinant.

7. The use of any one of claims 1-6, wherein the second HBcAg polypeptide, or immunogenic fragment thereof, comprises at least one HBcAg determinant and the second HBsAg polypeptide, or immunogenic fragment thereof, comprises at least one HBsAg determinant.

8. The use or of claim 6 or 7, wherein the ~~first and/or second~~ at least one HBsAg determinant of the first HBsAg polypeptide and/or the at least one HBsAg determinant of the second HBsAg polypeptide comprises an amino acid sequence at least 90% identical to amino acids 124 to

147 of SEQ ID NO: 22; or an amino acid sequence at least 90% identical to amino acids 99 to 168 of SEQ ID NO: 23.

9. The use of claim 6 or 7, wherein the ~~first and/or second~~at least one HBcAg determinant of the first HBcAg polypeptide and/or the at least one HBcAg determinant of the second HBcAg polypeptide comprises: an amino acid sequence comprising amino acid residue 80 of SEQ ID NO: 24; an amino acid sequence at least 90% identical to at least amino acids 70 to 90 of SEQ ID NO: 24; an amino acid sequence comprising amino acid residue 138 of SEQ ID NO: 24; an amino acid sequence at least 90% identical to at least amino acids 128 to 143 of SEQ ID NO: 24; an amino acid sequence at least 90% identical to at least 40, 50, 60, 70, 80, 90, or 100 contiguous amino acids of SEQ ID NO: 24; or an amino acid sequence at least 90% identical to amino acids 18 to 143 of SEQ ID NO: 24.

10. The use of any one of claims 1-9, wherein the protein-based HBV vaccine is to be administered to the subject at a dose of ~~about~~ 0.1 μg to ~~about~~ 1.0 mg of the first HBcAg polypeptide, or immunogenic fragment thereof, and a dose of ~~about~~ 0.1 μg to ~~about~~ 1.0 mg of the first HBsAg polypeptide, or immunogenic fragment thereof.

11. The use of any of claims 1-10, wherein the protein-based HBV vaccine further comprises an adjuvant.

12. The use of claim 11, wherein the adjuvant is monophosphoryl lipid A (MPL), poly(I:C), polyICLC adjuvant, CpG DNA, a STING agonist, c-di-AMP, c-di-GMP, c-di-CMP; short, blunt-ended 5′-triphosphate dsRNA (3pRNA) Rig-I ligand, poly[di(sodiumcarboxylatoethylphenoxy)phosphazene] (PCEP)), alum, virosomes, cytokines, IL-12, AS02, AS03, AS04, MF59~~, ISCOMATRIX® (a saponin-based adjuvant), IC31® (a two-component adjuvant comprising an antibacterial peptide and a synthetic ODN1a)~~, or Rig-I ligand.

13. The use of any of claims 1-12, wherein a dose of the protein-based HBV vaccine is to be administered to the subject: at least two times; no more than once every two weeks; no sooner than the day on which a final dose of the RNAi agent has been administered to the subject; on the same day as a final dose of the RNAi agent has been administered to the subject; no later than one month after a final dose of the RNAi agent has been administered to the subject; or no later than three months after a final dose of the RNAi agent has been administered to the subject.

14. The use of any of claims 1-13, wherein the nucleic acid-based HBV vaccine comprises at least one expression vector construct encoding the second HBcAg polypeptide, or

immunogenic fragment thereof, and the second HBsAg polypeptide, or immunogenic fragment thereof.

15. The use of claim 14, wherein the at least one expression construct comprises (a) a promoter that promotes expression of the second HBcAg polypeptide, or immunogenic fragment thereof, and the second HBsAg polypeptide, or immunogenic fragment thereof; or (b) a first and second promoter, the first promoter promoting expression of the second HBcAg polypeptide, or immunogenic fragment thereof, and the second promoter promoting expression of the second HBsAg polypeptide, or immunogenic fragment thereof.

16. The use of claim 15 wherein at least one the promoters is selected from the group consisting of a respiratory syncytial virus (RSV) promoter, a cytomegalovirus (CMV) promoter, a PH5 promoter, and an H1 promoter.

17. The use of any of claims 1-16, wherein the expression construct comprises a viral vector.

18. The use of claim 17, wherein the viral vector is selected from the group consisting of an adenovirus vector; a retrovirus vector, a lentiviral vector, a moloney murine leukemia virus vector,an adeno- associated virus vector; a herpes simplex virus vector; a SV 40 vector; a polyoma virus vector; a papilloma virus vector; a picornavirus vector; a pox virus vector, an orthopox virus vector, a vaccinia virus vector, a modified vaccinia virus Ankara (MVA) vector, an avipox vector, a canary pox vector, a fowl pox vector, and an Epstein Barr virus vector.

19. The use of any one of claims 1-18, wherein the nucleic acid-based HBV vaccine is to be administered to the subject at a tissue-culture infectious dose ($TCID_{50}$) of 10^6 to 10^{10} $TCID_{50}$; or 10^6 to 10^9 $TCID_{50}$; or 10^6 to 10^8 $TCID_{50}$.

20. The use of any of claims 1-19, wherein (a) a dose of the nucleic acid-based HBV vaccine is to be administered to the subject no sooner than two weeks after administration of a final dose of the protein-based vaccine is to be administered to the subject; (b) a first dose of the nucleic acid-based HBV vaccine is to be administered to the subject when the level of HBsAg in the serum of the subject is further decreased to at least 0.5 log 10 IU/ml following administration of at least one dose of the protein-based HBV vaccine; or (c) a single dose of the nucleic acid-based HBV vaccine is to be administered to the subject.

21. The use of any of claims 1-20, further, comprising that a nucleot(s)ide analog is also to be administered to the subject.

22. The use of claim 21, wherein at least one dose of the nucleot(s)ide analog is to be administered to the subject prior to administration of the RNAi agent to the subject; or multiple doses of the nucleot(s)ide analog are to be administered to the subject.

23. The use of claim 21 or 22, wherein the nucleot(s)ide analog is Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide (TAF), Lamivudine, Adefovir dipivoxil, Entecavir (ETV), Telbivudine, AGX-1009, emtricitabine, clevudine, ritonavir, dipivoxil, lobucavir, famvir, FTC, N-Acetyl-Cysteine (NAC), PC1323, theradigm-HBV, thymosin-alpha, and ganciclovir, besifovir (ANA-380/LB-80380), or tenofvir-exaliades (TLX/CMX157).

24. The use of any of claims 1-23, further comprising that an immune stimulator is also to be administered to the subject.

25. The use of claim 24, wherein immune stimulator is pegylated interferon alfa 2a (PEG-IFN-alpha-2a), Interferon alfa-2b, PEG-IFN-alpha-2b, Interferon lambda a recombinant human interleukin-7, and a Toll-like receptor 3, 7, 8 or 9 (TLR3, TLR7, TLR8, TLR9) agonist, a viral entry inhibitor, Myrcludex, an oligonucleotide that inhibits the secretion or release of HBsAg, REP 9AC, a capsid inhibitor, Bay41-4109, NVR-1221, a cccDNA inhibitor, IHVR-25,~~)~~ a viral capsid, an MVA capsid, an immune checkpoint regulator, an CTLA-4 inhibitor, ipilimumab, a PD-1 inhibitor, Nivolumab, Pembrolizumab, BGB-A317 antibody, a PD-L1 inhibitor, atezolizumab, avelumab, durvalumab, or an affimer biotherapeutic.

26. The use of any one of claims 1-25, wherein the subject is human.

27. The use of any of claims 1-26, wherein

(a) the RNAi agent comprises at least one modified nucleotide;

(b) substantially all of the nucleotides of said sense strand and substantially all of the nucleotides of said antisense strand are modified nucleotides, wherein said sense strand is conjugated to a ligand attached at the 3'-terminus;

(c) the RNAi agent comprises a 3' overhang of at least 1 nucleotide or at least 2 nucleotides;

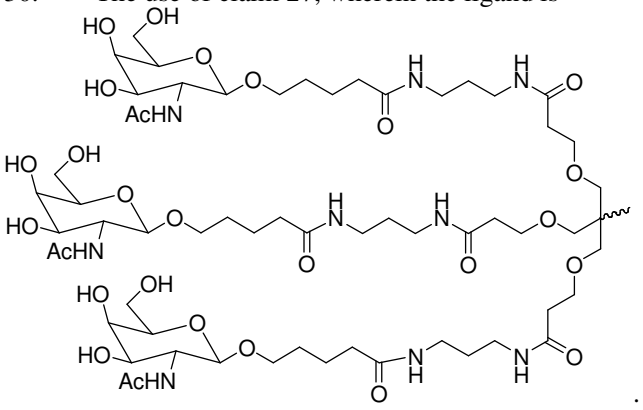
(d) the double-stranded region of the RNAi agent is 15-30, 17-23, 17-25, 23-27, 19-21, or 21-23 nucleotide pairs in length; or

(e) each strand of the RNAi agent has 15-30 or 19-30 nucleotides.

28. The use of claim 27, wherein the ligand is one or more GalNAc derivatives attached through a monovalent linker, bivalent branched linker, or trivalent branched linker.

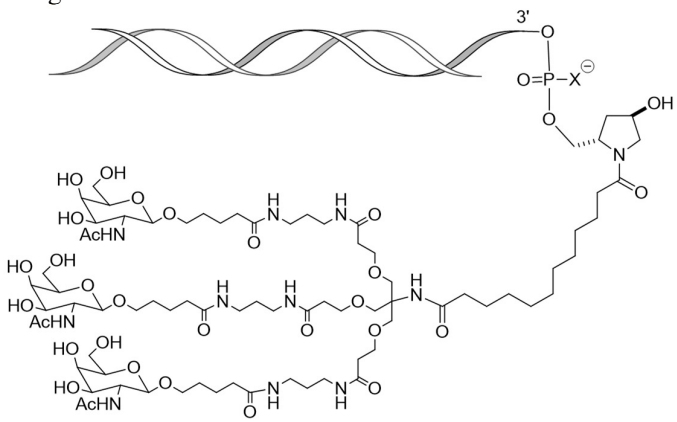
29. The use of claim 28, wherein at least one of said modified nucleotides is a deoxy-nucleotide, a 3’-terminal deoxy-thymine (dT) nucleotide, a 2'-O-methyl modified nucleotide, a 2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an unlocked nucleotide, a conformationally 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’-hydroxyl-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, or a nucleotide comprising a 5’-phosphate mimic.

30. The use of claim 27, wherein the ligand is



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31. The use of claim 30, wherein the RNAi agent is conjugated to the ligand as shown in the following schematic



wherein X is O or S.

32. The use of any of claims 1-26, wherein (i) the sense strand comprises the nucleotide sequence of 5'-gsusguGfcAfCfUfucgcuucacaL96-3' (SEQ ID NO: 37) and the antisense strand

comprises the nucleotide sequence of 5'-usGfsugaAfgCfGfaaguGfcAfcacsusu-3' (SEQ ID NO: 30), or (ii) the sense strand comprises the nucleotide sequence of 5'-csasccauGfcAfAfCfuuuuucaccuL96-3' (SEQ ID NO: 38) and the antisense strand comprises the nucleotide sequence of 5'-asGfsgugAfaAfAfaguuGfcAfuggugsusu-3' (SEQ ID NO: 32);

wherein a, c, g, and u are 2'-O-methyl (2'-OMe) A, 2'-OMe C, 2'-OMe G, and 2'-OMe U, respectively; Af, Cf, Gf, and Uf are 2'-fluoro A, 2'-fluoro C, 2'-fluoro G, and 2'-fluoro U, respectively; s is a phosphorothioate linkage; and L96 is N-[tris(GalNAc-alkyl)-amidodecanoyl)]-4-hydroxyprolinol.

33. The use of any of claims 1-32, wherein the first or second HBcAg polypeptide, or immunogenic fragment thereof, and/or the first or second HBsAg polypeptide, or immunogenic fragment thereof, comprise at least one determinant present in at least four, at least six, or at least seven genotypes of HBV.

~~34. A kit for treating a subject having an HBV infection, the kit comprising:~~

~~a) an RNAi agent that inhibits expression of at least three HBV transcripts, wherein the RNAi agent comprises a sense strand and an antisense strand forming a double stranded region, and (i) the sense strand comprises the nucleotide sequence of 5' GUGUGCACUUCGCUUCACA 3' (SEQ ID NO: 27) and the antisense strand comprises the nucleotide sequence of 5'-UGUGAAGCGAAGUGCACACUU-3' (SEQ ID NO: 25), or (ii) the sense strand comprises the nucleotide sequence of 5' CACCAUGCAACUUUUUCACCU 3' (SEQ ID NO: 28) and the antisense strand comprises the nucleotide sequence of 5' AGGUGAAAAAGUUGCAUGGUGUU 3' (SEQ ID NO: 26);~~

~~b) a protein-based vaccine comprising a first HBV core antigen (HBcAg) polypeptide, or immunogenic fragment thereof, and a first HBV surface antigen (HBsAg) polypeptide, or immunogenic fragment thereof; and~~

~~c) a nucleic acid-based vaccine comprising an expression vector construct encoding a second HBcAg polypeptide, or immunogenic fragment thereof, and/or a second HBsAg polypeptide, or immunogenic fragment thereof,~~

~~wherein the second HBcAg polypeptide, or immunogenic fragment thereof, and/or the second HBsAg polypeptide, or immunogenic fragment thereof, shares at least one epitope with at least one of the first HBcAg polypeptide, or immunogenic fragment thereof, and/or the first HBsAg polypeptide, or immunogenic fragment thereof; and~~

~~d) instructions for use according to the uses of any one of claims 1-33.~~