CLAIMS

What is claimed is:

1. A multi-specific antigen binding molecule that binds to human CD3 and HIV gp120, wherein the antigen binding molecule comprises:

(a) a first antigen binding domain that comprises a first heavy chain variable domain (VH) and a first light chain variable domain (VL), wherein the first antigen binding domain binds to CD3; and

(b) a second antigen binding domain that binds to HIV gp120 comprising one or more extracellular (EC) domain of CD4, wherein the one or more EC domains of CD4 comprise a sequence as set forth below, or a sequence that is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from the group consisting of:

(i) KKVVYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRVDSR RSLWDQGNFPLIIKNLKPEDSDTYICEVEDQKEEVQLVVVG (SEQ ID NO: 746);

(ii) KKVVYGKKGDTVELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRVDSR RSLWDQGNFPLIIKNLKPEDSDTYICEVEDQKEEVQLVVVGGGGSGKKVVYGKKGDTV ELTCTASQKKNIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRVDSRRSLWDQGNFPLI IKNLKPEDSDTYICEVEDQKEEVQLVVVG (SEQ ID NO: 747);

(iii) KKVVLGKKGDTVELTCTASQKKSIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRADSR RSLWDQGNFPLIIKNLKIEDSDTYICEVEDQKEEVQLLVFG (SEQ ID NO: 748); or

(iv) KKVVLGKKGDTVELTCTASQKKSIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRADSR RSLWDQGNFPLIIKNLKIEDSDTYICEVEDQKEEVQLLVFGGGGSGKKVVLGKKGDTV ELTCTASQKKSIQFHWKNSNQIKILGNQGSFLTKGPSKLNDRADSRRSLWDQGNFPLI IKNLKIEDSDTYICEVEDQKEEVQLLVFG(SEQ ID NO: 749).

2. The multi-specific antigen binding molecule of claim 1, wherein the one or more EC domains of CD4 comprise a sequence as set forth below, or a sequence that is at

least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the sequence of SEQ ID NO: 746.

3. The multi-specific antigen binding molecule of claim 1 or 2, wherein the first antigen binding domain comprises:

a) a first VH-complementarity determining region (CDR) 1 (VH-CDR1), a first VH-CDR2, a first VH-CDR3, a first VL-CDR1, a first VL-CDR2 and a first VL-CDR3 comprising the following amino acid sequences, respectively (according to Kabat): SEQ ID NOs: 1, 11, 8, 4, 9 and 10; or SEQ ID NOs: 1, 12, 8, 4, 9 and 10; and

b) a second antigen binding domain comprises one or more EC domains of CD4 comprising an amino acid sequence that comprises or is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to a CD4 EC domain selected from the group consisting of SEQ ID NOs: 746-749.

4. The multi-specific antigen binding molecule of any one of claims 1 to 3, wherein the first antigen binding domain comprises a first VH-CDR1, a first VH-CDR2, a first VH-CDR3, a first VL-CDR1, a first VL-CDR2 and a first VL-CDR3 comprising the following amino acid sequences, respectively (according to Kabat): SEQ ID NOs: 1, 12, 8, 4, 9 and 10; and the second antigen binding domain comprises one or more EC domains of CD4 comprising an amino acid sequence that comprises or is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to a CD4 EC domain selected from the group consisting of SEQ ID NO: 746.

5. The multi-specific antigen binding molecule of any one of claims 1 to 4, wherein the first antigen binding domain comprises a first VH and a first VL comprising the amino acid sequences set forth, respectively, or comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequences set forth, respectively: SEQ ID NOs: 51 and 56; and the second antigen binding

domain comprises one EC domain of CD4 comprising an amino acid sequence that comprises or is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, identical to a CD4 EC domain of SEQ ID NO: 746.

6. The multi-specific antigen binding molecule of claim 5, wherein the first antigen binding domain comprises a first VH and a first VL comprising the amino acid sequences set forth, respectively: SEQ ID NOs: 51 and 56; and the second antigen binding domain comprises one EC domain of CD4 comprising an amino acid sequence of SEQ ID NO: 746.

7. The multi-specific antigen binding molecule of any one of claims 1 to 6, comprising a heterodimeric human IgG1 or IgG4, comprising a first Fc region and a second Fc region, wherein one or both of the first and second Fc regions comprise one or more of the following amino acids at the indicated positions (EU numbering):

(i) Alanine at position 234

(ii) Alanine at position 235; and

(iii) Serine at position 331.

8. The multi-specific antigen binding molecule of any one of claims 1 to 7, comprising a heterodimeric human IgG1 or IgG4, comprising a first Fc region and a second Fc region, wherein one or both of the first and second Fc regions comprise the following amino acids at the indicated positions (EU numbering):

(i) Tyrosine at position 252, threonine at position 254 and glutamic acid at position 256 (YTE); or

(ii) Leucine at position 428 and serine at position 434 (LS).

9. The multi-specific antigen binding molecule of any one of claims 1 to 8, comprising a heterodimeric human IgG1, comprising a first Fc region and a second Fc region, wherein both of the first and second Fc regions comprise the following amino acids at the indicated positions (EU numbering): Tyrosine at position 252, threonine at position 254 and glutamic acid at position 256 (YTE).

10. The multi-specific antigen binding molecule of any one of claims 1 to 9, comprising a heterodimeric human IgG1 or IgG4, comprising a first Fc region and a second Fc region, comprising the following amino acids at the indicated positions (EU numbering):

(i) the first Fc region comprises a tryptophan at position 366 (T366W); and the second Fc region comprises a serine at position 366 (T366S), an alanine at position 368 (L368A) and a valine at position 407 (Y407V);

(ii) the first Fc region comprises a serine at position 366 (T366S), an alanine at position 368 (L368A) and a valine at position 407 (Y407V); and the second Fc region comprises a tryptophan at position 366 (T366W);

(iii) the first Fc region comprises a cysteine at position 354 (S354C), a tryptophan at position 366 (T366W); and the second Fc region comprises a cysteine at position 349 (Y349C), a serine at position 366 (T366S), an alanine at position 368 (L368A) and a valine at position 407 (Y407V);

(iv) the first Fc region comprises cysteine at position 349 (Y349C), a serine at position 366 (T366S), an alanine at position 368 (L368A) and a valine at position 407 (Y407V); and the second Fc region comprises a cysteine at position 354 (S354C), a tryptophan at position 366 (T366W).

11. The multi-specific antigen binding molecule of any one of claims 1 to 10, comprising a heterodimeric human IgG1, comprising a first Fc region and a second Fc region, comprising the following amino acids at the indicated positions (EU numbering): the first Fc region comprises a serine at position 366 (T366S), an alanine at position 368 (L368A) and a valine at position 407 (Y407V); and the second Fc region comprises a tryptophan at position 366 (T366W).

12. The multi-specific antigen binding molecule of any one of claims 1 to 11, comprising a heterodimeric human IgG1 or IgG4, comprising a first Fc region and a second Fc region, wherein one of the first Fc region or the second Fc region comprise the following amino acids at the indicated positions (EU numbering):

(i) arginine at position 435 (H435R); or

(ii) arginine at position 435 (H435R) and phenylalanine at position 436 (Y436F).

13. The multi-specific antigen binding molecule of any one of claims 1 to 12, comprising a heterodimeric human IgG1 or IgG4, comprising a first Fc region and a second Fc region, comprising the following amino acids at the indicated positions (EU numbering):

(i) the first Fc region comprises an alanine at position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S) and a tryptophan at position 366 (T366W); and the second Fc region comprises an alanine a position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S), a serine at position 366 (T366S), an alanine at position 368 (L368A), a valine at position 407 (Y407V), and an arginine at position 435 (H435R);

(ii) the first Fc region comprises an alanine at position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S) and a tryptophan at position 366 (T366W); and the second Fc region comprises an alanine a position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S), a serine at position 366 (T366S), an alanine at position 368 (L368A), a valine at position 407 (Y407V), an arginine at position 435 (H435R) and a phenylalanine at position 436 (Y436F);

(iii) the first Fc region comprises an alanine at position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S), a serine at position 366 (T366S), an alanine at position 368 (L368A), and a valine at position 407 (Y407V); and the second Fc region comprises an alanine at position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S) and a tryptophan at position 366 (T366W);

(iv) the first Fc region comprises an alanine at position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S), a tryptophan at position 366 (T366W), a leucine at position 428 (M428L) and a serine at position 434 (N434S); and the second Fc region comprises an alanine a position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S), a serine at position 366 (T366S), an alanine at position 368 (L368A), a valine at position 407 (Y407V), and an arginine at position 435 (H435R); or

(v) the first Fc region comprises an alanine at position 234 (L234), an alanine at position 235 (L235A), a serine at position 331 (P331S), a tryptophan at position 366 (T366W), a tyrosine at position 252 (M252Y), a threonine at position 254 (S254T) and a glutamic acid at position 256 (T256E); and the second Fc region comprises an alanine a position 234 (L234), an

alanine at position 235 (L235A), a serine at position 331 (P331S), a serine at position 366 (T366S), an alanine at position 368 (L368A), a valine at position 407 (Y407V), and an arginine at position 435 (H435R).

14. The multi-specific antigen binding molecule of any one of claims 1 to 13, wherein the first antigen binding domain is a Fab and the second antigen binding domain is a scFv or an EC domain of CD4 wherein the first antigen binding domain comprises a first HC and a LC, and the second antigen binding domain comprises a second HC, the second HC, the first HC and the LC comprising the amino acid sequences set forth, respectively, below, or comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequences set forth, respectively, below:

1) SEQ ID NOs: 751, 752 and 753;
2) SEQ ID NOs: 754, 752 and 753;
3) SEQ ID NOs: 755, 756 and 753;
4) SEQ ID NOs: 755, 757 and 753;
5) SEQ ID NOs: 758, 757 and 753; or
6) SEQ ID NOs: 759, 756 and 753.

15. The multi-specific antigen binding molecule of any one of claims 1 to 14, wherein the first antigen binding domain is a Fab and the second antigen binding domain is a scFv or an EC domain of CD4 wherein the first antigen binding domain comprises a first HC and a LC, and the second antigen binding domain comprises a second HC, the second HC, the first HC and the LC comprising the amino acid sequences set forth, respectively, below, or comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequences set forth, respectively, below:

1) SEQ ID NOs: 751, 752 and 753; or
2) SEQ ID NOs: 755, 756 and 753.

16. The multi-specific antigen binding molecule of any one of claims 1 to 15, wherein the first antigen binding domain is a Fab and the second antigen binding domain is an

EC domain of CD4 wherein the first antigen binding domain comprises a first HC and a LC, and the second antigen binding domain comprises a second HC, the second HC, the first HC and the LC comprising amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequences set forth, respectively: SEQ ID NOs: 751, 752 and 753.

17. The multi-specific antigen binding molecule of any one of claims 1 to 16, wherein the first antigen binding domain is a Fab and the second antigen binding domain is an EC domain of CD4 wherein the first antigen binding domain comprises a first HC and a LC, and the second antigen binding domain comprises a second HC, the second HC, the first HC and the LC comprising the amino acid sequences set forth, respectively: SEQ ID NOs: 751, 752 and 753.

18. The multi-specific antigen binding molecule of any one of claims 1 to 17, wherein the multi-specific antigen binding molecule is a bispecific antigen binding molecule.

19. The multi-specific antigen binding molecule of any one of claims 1 to 18, wherein the first antigen binding domain binds to CD3 with a KD of lower 3.0 nM (*e.g.*, 2.5 nM), and the antigen binding molecule has a serum half-life in a human or cynomolgus monkey of at least 7 days.

20. A polynucleotide or multiple polynucleotides encoding the HC and LC of the first antigen binding domain that is a Fab, and the HC of the second antigen binding domain that is an scFv or an EC domain of CD4, of the multi-specific antigen binding molecule of any one of claims 1 to 18.

21. The polynucleotide or polynucleotides of claim 20, encoding a multi-specific antigen binding molecule of any one of claims 1 to 18, comprising the following polynucleotide sequences, or polynucleotide sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the polynucleotide sequences set forth, respectively, below:

i. SEQ ID NOs: 995, 996 and 997;

ii. SEQ ID NOs: 998, 999 and 1000;
iii. SEQ ID NOs: 1001, 1002 and 1003;
iv. SEQ ID NOs: 1004, 1005 and 1000;
v. SEQ ID NOs: 1006, 1002 and 997;
vi. SEQ ID NOs: 1007, 1093 and 1000;
vii. SEQ ID NOs: 998, 1008 and 1000;
viii. SEQ ID NOs: 998, 1009 and 1000;
ix. SEQ ID NOs: 1010, 1011 and 1012;
x. SEQ ID NOs: 1013, 1014 and 1015;
xi. SEQ ID NOs: 1016, 1017 and 1012;
xii. SEQ ID NOs: 1018, 1019 and 1012;
xiii. SEQ ID NOs: 1018, 1020 and 1012;
xiv. SEQ ID NOs: 1021, 1022 and 1023; or
xv. SEQ ID NOs: 1024, 1025 and 1023.

22. The polynucleotide or polynucleotides of claim 20 or 21, comprising the following polynucleotide sequences, or polynucleotide sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the polynucleotide sequences set forth, respectively: SEQ ID NOs: 995, 996 and 997.

23. The polynucleotide or polynucleotides of claim 22, comprising the following polynucleotide sequences, respectively: SEQ ID NOs: 995, 996 and 997.

24. The polynucleotide or polynucleotides of claim 20 or 21, comprising the following polynucleotide sequences, or polynucleotide sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the polynucleotide sequences set forth, respectively: SEQ ID NOs: 998, 999 and 1000.

25. The polynucleotide or polynucleotides of claim 24, comprising the following polynucleotide sequences, respectively: SEQ ID NOs: 998, 999 and 1000.

26. The polynucleotide or polynucleotides of any one of claims 20 to 25, wherein the polynucleotide or polynucleotides are comprised of DNA or RNA.

27. The polynucleotide or polynucleotides of any one of claims 20 to 26, wherein the polynucleotide or polynucleotides are comprised of mRNA.

28. An expression cassette or multiple expression cassettes comprising one or more regulatory sequences operably linked to the polynucleotide or polynucleotides of any one of claims 20 to 27.

29. An expression vector or multiple expression vectors comprising one or more regulatory sequences operably linked to the polynucleotide or polynucleotides of any one of claims 20 to 27, or the expression cassette or expression cassettes of claim 28.

30. The expression vector or expression vectors of claim 29, wherein the expression vector or expression vectors comprise a plasmid vector or a viral vector.

31. The expression vector or expression vectors of claim 29 or 30, wherein the expression vector comprises:

(i) a first expression cassette comprising a first polynucleotide encoding an anti-CD3 VL-CL fusion protein;

(ii) a second expression cassette comprising a second polynucleotide encoding an anti-CD3 VH-Fc fusion protein; and

(iii) a third expression cassette comprising a third polynucleotide encoding a CD4 extracellular (EC) domain-Fc fusion protein.

32. The expression vector of claim 31, wherein the anti-CD3 VL-CL fusion protein, the anti-CD3 VH-Fc fusion protein and the CD4 EC domain-Fc fusion protein comprise amino acid sequences set forth, respectively, or comprise amino acid sequences that are at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the amino acid sequences set forth, respectively: SEQ ID NOs: 753, 752 and 751.

33. The expression vector of claim 32, wherein the anti-CD3 VL-CL fusion protein, the anti-CD3 VH-Fc fusion protein and the CD4 EC domain-Fc fusion protein comprise amino acid sequences set forth, respectively: SEQ ID NOs: 753, 752 and 751.

34. The expression vector of any one of claims 29 to 33, wherein the first, second and third expression cassettes each comprise a promoter of equivalent transcription strength, *e.g.*, a constitutive promoter, *e.g.*, a promoter selected from cytomegalovirus (CMV), SV40, RSV, EF1a, UBC, PGK and CAGG.

35. A cell or population of cells, comprising the polynucleotide or polynucleotides of any one of claims 20 to 27, the expression cassette or multiple expression cassettes of claim 28, or the expression vector or expression vectors of any one of claims 29 to 34.

36. The cell or population of cells of claim 35, wherein the cell or population of cells comprises a eukaryotic cell.

37. A pharmaceutical composition comprising one or more multi-specific antigen binding molecules claimed in any one of claims 1 to 19, and a pharmaceutically acceptable carrier.

38. The pharmaceutical composition of claim 37, wherein the composition comprises an aqueous formulation.

39. The pharmaceutical composition of claim 37 or 38, at a concentration of from 0.1 mg/ml to 150 mg/ml, *e.g.*, 0.1 mg/ml to 100 mg/ml, *e.g.*, 1 mg/ml to 100 mg/ml, *e.g.*, from 5 mg/ml to 60 mg/ml, *e.g.*, from 20 mg/ml to 150 mg/ml, or from 10 mg/ml to 50 mg/ml.

40. The pharmaceutical composition of any one of claims 37 to 39, formulated for intravenous, intramuscular or subcutaneous administration.

41. A kit comprising one or more containers comprising one or more of the multi-specific antigen binding molecules claimed in any one of claims 1 to 19, the polynucleotide or polynucleotides of any one of claims 20 to 27 the expression vector or

expression vectors of any one of claims 29 to 34, or the pharmaceutical composition of any one of claims 37 to 40.

42. The kit of claim 41, comprising one or more unitary doses of the one or more multi-specific antigen binding molecules, or the polynucleotide or polynucleotides, in one or more containers.

43. The kit of claim 41 or 42, comprising one or more unitary doses of the one or more multi-specific antigen binding molecules and a second agent for treating an HIV infection in separate containers.

44. The kit of claim 43, further comprising at least one of a toll-like receptor (TLR) agonist and an IL-15 receptor agonist.

45. The kit of claim 44, comprising a TLR7 agonist selected from the group consisting of vesatolimod, imiquimod, and resiquimod.

46. The kit of any one of claims 41 to 45, wherein the first multi-specific antigen binding molecule comprises an EC domain of CD4, and the second or additional antigen binding molecules comprise VH and VL regions from an antibody selected from the group consisting of 10-1074, 10-1074-J, GS-9722 (elipovimab), GS-2872, PGT-121, PGT-121.66, PGT-121.414 and PGT-134.

47. The kit of any one of claims 41 to 46, further comprising second or additional antigen binding molecules comprising VH and VL regions from an antibody selected from the group consisting of GS-9723, GS-5423, 3BNC117, VRC07 and VRC07-523.

48. The kit of any one of claims 41 to 47, comprising:

(i) a multi-specific antigen binding molecule comprising an EC domain of CD4 of any one of claims 1 to 19;

(ii) an antibody or multi-specific antigen binding molecule that comprises VH and VL regions from an antibody selected from the group consisting of 10-1074, 10-1074-J, GS-9722 (elipovimab), GS-2872, PGT-121, PGT-121.66, PGT-121.414 and PGT-134; and

(iii) an antibody or multi-specific antigen binding molecule that comprises VH and VL regions from an antibody selected from the group consisting of GS-9723, GS-5423, 3BNC117, VRC07 and VRC07-523.

49. A method of producing a multi-specific antigen binding molecule, the method comprising:

a) culturing a cell or population of cells of claim 35 or 36 transformed with the polynucleotide or polynucleotides of any one of claims 20 to 27, or the expression cassette or multiple expression cassettes of claim 28 in a cell culture under conditions sufficient to express the multi-specific antigen binding molecules; and

b) isolating or purifying the antigen binding molecules from the cell culture.

50. Use of the multi-specific antigen binding molecule or antigen binding fragment thereof of any one of claims 1 to 19, one or more polynucleotides of any one of claims 20 to 27, or the pharmaceutical composition of any one of claims 37 to 40 in the manufacture of a medicament for treating or preventing HIV in a human subject in need thereof.

51. The use of claim 50, wherein the medicament further comprises a second agent for treating an HIV infection.

52. The use of claim 50 or 51, wherein the medicament further comprises at least one of a TLR agonist and an IL-15 receptor agonist.

53. The use of any one of claims 50 to 52, wherein the first multi-specific antigen binding molecule comprises an EC domain of CD4, and the second antigen binding molecule comprises VH and VL regions from an antibody selected from the group consisting of 10-1074, 10-1074-J, GS-9722 (elipovimab), GS-2872, PGT-121, PGT-121.66, PGT-121.414 and PGT-134.

54. The use of any one of claims 50 to 53, wherein the medicament further comprises an additional antigen binding molecule that comprises VH and VL regions from an antibody selected from the group consisting of GS-9723, GS-5423, 3BNC117, VRC07 and VRC07-523.

55. The use of claim 50, wherein the medicament comprises:

(i) a multi-specific antigen binding molecule of any one of claims 1 to 19;

(ii) an antibody or multi-specific antigen binding molecule that comprises VH and VL regions from an antibody selected from the group consisting of 10-1074, 10-1074-J, GS-9722 (elipovimab), GS-2872, PGT-121, PGT-121.66, PGT-121.414 and PGT-134; and

(iii) an antibody or multi-specific antigen binding molecule that comprises VH and VL regions from an antibody selected from the group consisting of GS-9723, GS-5423, 3BNC117, VRC07 and VRC07-523.