HUMAN IMMUNODEFICIENCY VIRUS VACCINE

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ABSTRACT
The present invention relates, in general, to human immunodeficiency virus (HIV) and, in particular, to an HLA-based HIV vaccine.
Figure 1. C4-V3 Th-CTL Peptides Induce HLA B7 Reactive CD8+ CTL in Normal HIV-1 Seronegative Humans. Panels A, B, C show specific lysis from in vivo immunization and in vitro restimulation against each of the V3 B7 CTL epitope variants. BLCL lymphoblastoid cell line (BLCL) as peptide coating control. C4-C4 Th2 determinant peptide on BLCL, V3MN, V3RF, V3EV91, VJCana are the B7 CTL epitope variant peptide coated on BLCL. Data show patients in Panel A responded to 1 of 4 B7 CTL epitope variants (the HIV EV91 variant) while the patient in Panel C responded to 3 of 4 B7 epitope variants (HIVMN, EV91 and Cana). Panels B and D show 2 HLA B7 negative individuals that made no CTL response to the B7-restricted CTL peptide immunogen after both in vivo immunization and in vitro restimulation.
HUMAN IMMUNODEFICIENCY VIRUS VACCINE

[0001] This is a continuation-in-part of application Ser. No. 08/497,497, filed Feb. 4, 2000, now pending, the entire contents of which is incorporated herein by reference.

TECHNICAL FIELD

[0002] The present invention relates, in general, to human immunodeficiency virus (HIV) and, in particular, to an HLA-based HIV vaccine.

BACKGROUND

[0003] As the HIV epidemic continues to spread worldwide, the need for an effective HIV vaccine remains urgent. The extraordinary ability of HIV to mutate, the inability of many currently known specificities of anti-HIV antibodies to consistently neutralize HIV primary isolates, and the lack of a complete understanding of the correlates of protective immunity to HIV infection have impeded efforts to develop an HIV vaccine having the desired effectiveness.

[0004] Although a majority of HIV-infected subjects develop acquired immunodeficiency syndrome (AIDS), approximately 10-15% of patients are AIDS-free after 10 years of infection, and are termed non-progressors to AIDS (Sheppard et al., AIDS 7:1159-66 (1993), Phair, AIDS Res. Human Retroviruses 10:883-885 (1994)). Of those that do develop AIDS, those that do develop AIDS, approximately 10% of HIV-infected patients progress to AIDS within the first two to three years of HIV infection, and are termed rapid progressors to AIDS (Sheppard et al., AIDS 7:1159-66 (1993), Phair, AIDS Res. Human Retroviruses 10:883-885 (1994)). The initial characterization of anti-HIV immune responses in non-progressors and rapid progressors to AIDS has provided some insight into what may be the correlates of protective immunity to HIV.


[0006] It has been suggested that less effective anti-HIV CD8+ CTL responses may be oligoclonal regarding TCR Vβ usage and targeted at several non-immunodominant HIV CTL epitopes, whereas more effective anti-HIV CTL responses may be polyclonal and targeted at fewer immunodominant epitopes (Rowland-Jones et al, Nature Medicine 1:59-64 (1995), Nowak et al, Nature 375:606-611 (1995)). Taken together with data that suggest the inheritance of certain HLA-encoded or other host genes may be associated with either rapid progression or non-progression to AIDS (Haynes et al, Science 271:324-328 (1996)), these data suggest that host gene expression may determine the quality and/or quantity of host anti-HIV immune responses.

[0007] Potent non-HLA restricted CD8+ T cell anti-HIV activity that suppresses the ability of HIV to replicate has been described by Levy et al (Walker et al, Science 234:1563-1566 (1986)). This CD8+ "HIV suppressor" activity is initially present in rapid progressors, then declines with the onset of AIDS (Walker et al, Science 234:1563-1566 (1986)), and may be mediated in part by cytokines such as IL-10 (Batrak et al, Nature 378:563 (1995)), and by the chemokines, RANTES, MIP-1α and MIP-1β (Cocchi et al, Science 270:1811-1815 (1995)). Berger and colleagues have recently discovered a novel host molecule termed Fasun, that is required for T cell tropic HIV to infect CD4+ T cells, and has significant homology with a known chemokine receptor, the IL8 receptor (Feng et al, Science 272:872-877 (1996)).

[0008] Thus, for induction of CD8+ "HIV suppressor" cells, CD8+ CTL and CD4+ T helper cells by an HIV immunogen, what is most likely needed are immunogens that induce these anti-HIV responses to a sufficient number of HIV variants such that a majority of HIV variants in a geographic area will be recognized.

[0009] A key obstacle to HIV vaccine development is the extraordinary variability of HIV and the rapidity and extent of HIV mutation (Wain-Hobson in The Evolutionary biology of Retroviruses, SSB Morse Ed. Raven Press, NY, pgs 185-209 (1994)). Recent data in patients treated with antiretroviral drugs have demonstrated that HIV variants emerge rapidly after initiation of treatment and can be isolated from peripheral blood as early as 3 weeks after initiation of drug treatment (Wei et al, Nature 373:117-122 (1995), Ho et al, Nature 373:123 (1995)). Moreover, up to 109 new HIV virions are produced in an infected individual per day, and the half-life of HIV quasispecies is approximately 2 days (Wei et al, Nature 373:117-122 (1995), Ho et al, Nature 373:123 (1995)).

[0010] Myers, Korber and colleagues have analyzed HIV sequences worldwide and divided HIV isolates into groups or clades, and provided a basis for evaluating the evolutionary relationship of individual HIV isolates to each other (Myers et al (Eds), Human Retroviruses and AIDS (1995), Published by Theoretical Biology and Biophysics Group, T-10, Mail Stop K710, Los Alamos National Laboratory, Los Alamos, N. Mex. 87545). The degree of variation in HIV protein regions that contain CTL and T helper epitopes has also recently been analyzed by Korber et al, and sequence variation documented in many CTL and T helper epitopes among HIV isolates (Korber et al (Eds), HIV
Molecular Immunology Database (1995), Published by Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, N. Mex. 87545.

[0011] A new level of HIV variation complexity was recently reported by Hahn et al. by demonstrating the frequent recombination of HIV among clades (Robinson et al., J. Mol. Evol. 40:245-259 (1995)). These authors suggest that as many as 10% of HIV isolates are mosaics of recombination, suggesting that vaccines based on only one HIV clade will not protect immunized subjects from mosaic HIV isolates (Robinson et al, J. Mol. Evol. 40:245-259 (1995)).


SUMMARY OF THE INVENTION

[0013] The present invention relates to an HLA-based vaccine against HIV. Vaccines of the invention, which induce salutary anti-HIV immune responses, can be designed based on analysis of the HLA alleles present in the cohort to be immunized and analysis of the most common HIV variants present in the geographic location of the cohort. The invention also relates to a method of immunizing a patient against HIV using the HLA-based vaccine.

[0014] Objects and advantages of the present invention will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIGS. 1A-1D. C4-V3 Th-CTL Peptides Induce HLA B7 Reactive CD8+ CTL in Normal HIV-1 Seronegative Humans. FIGS. 1A and 1C show specific lyys from in vivo immunization and in vitro restimulation against each of the V3 B7 CTL epitope variants. BCL1-B lymphoblastoid cell (BCLC) no peptide control. C4-C4 Th determinant peptide on BCLC, V3MN, V3RE, V3EV91, and V3CanA0 are the B7 CTL epitope variant peptide coated on BCLC. Data show patient in FIG. 1A responded to 1 of 4 B7 CTL epitope variants (the HIV EV91 variant) while the patient in FIG. 1C responded to 3 of 4 B7 epitope variants (HIV MN, EV91 and CanA0). FIGS. 1B and 1D show 2 HLA B7 negative individuals that made no CTL response to the B7-restricted CTL peptide immunogen after both in vivo immunization and in vitro restimulation.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present invention relates to an HLA-based HIV vaccine. The invention further relates to a method of immunizing a patient against HIV by using such a vaccine.

[0017] The HLA-based vaccines of the invention can be designed based on available HLA databases. Results obtained in International Histocompatibility Testing Workshops, such as the most recent ones (Histocompatibility Testing 1980, Terakani (Ed.), UCLA Tissue Typing Laboratory, Los Angeles, Calif. (1980), Histocompatibility Testing 1984, Albert et al. (Eds.), Springer-Verlag, Berlin (1984), Immunobiology of HLA, 2 volumes, Dupont (Ed.), Springer-Verlag, New York, (1989), HLA 1991, 2 volumes, Tsuji et al. (Eds.), Oxford University Press, Oxford (1992), provide such a database.

[0018] The International Histocompatibility Workshop data (such as Histocompatibility Testing 1984, Albert et al (Eds.), Springer-Verlag, Berlin (1984), HLA 1991, 2 volumes, Tsuji et al. (Eds.), Oxford University Press, Oxford (1992)), supplemented with published data from selected laboratories (such as Williams et al., Human Immunol. 33:49-46 (1992), Chandrayangyag et al., In Proceedings of the Second As-a and Oceania Histocompatibility Workshop Conference, Simon et al. (Eds.), Immunopublishing, Toronto, pgs. 276-287 (1983)) provide an estimate of the frequencies of HLA alleles that have been shown to serve as restriction elements for HIV CTL epitopes (HIV Molecular Immunology Database (1995), Korber et al. (Eds.), Los Alamos National Laboratory: Published by Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, N. Mex. 87545). Table I summarizes these frequencies for the four populations. African Americans, North American Indians, USA Caucasians, and Thais, used here for purposes of exemplification. Section II of the Los Alamos HIV epitope database of Korber et al (HIV Molecular Immunology Database (1995), Los Alamos National Laboratory: Published by Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, N. Mex. 87545) lists the CTL epitopes by HLA restriction element. Using these two sets of data and the Hardy-Weinberg theorem (Hardy, Science 28:49-50 (1908)), the proportion of each of the four populations that would be predicted to present peptides to the immune system if a limited number of HIV epitopes were included in a vaccine designed specifically for that population can be estimated. A similar calculation for a vaccine designed to be immunogenic for all four populations has been made. These results are presented in Table 2.

[0019] The strategy that can be used in this analysis is to first identify the most frequent restriction elements in the population under consideration for vaccination (or common to the 4 populations), to identify peptides that are presented by more than one HLA allel, and then to seek commonality between these two lists. Probability calculations then utilize the frequencies of the commonality alleles supplemented by those of additional high frequency alleles in the population. Alleles can be added until the proportion of the individuals in the population carrying one or more of the alleles in the list is at an acceptable level, for instance, greater than 90% in the examples. The aim is to maximize the sum of the HLA gene frequencies that recognize the least number of different HIV peptides to be included in an HIV immunogen. The next step is to choose the peptides associated with the restricting allele. In some instances, only one peptide is associated with an allele while in others, multiple peptides are presented by the same allel.
Criteria that can be used choosing which immunogenic epitopes to be included in a preventive HIV immunogen are listed below:

1. Peptides reported to be immunogenic in situations thought to reflect protection from retroviral infection or protection from retroviral-induced immunodeficiency disease (ie, in non-progressors to AIDS).

2. Peptides presented to the immune system by HLA restricting elements reported to be associated with non progression to AIDS (for example, Haynes et al, Science 171:324-328 (1996)).

3. Peptides reported to be “immunodominant” stimulators of HLA class I-restricted anti-HIV CTL responses (Nowak et al, Nature 375:606-611 (1995)).

4. Peptides reported presented by several disparate HLA class I allotypes.

For the four population cohorts considered in detail here by way of example, as few as 2 and as many as 5 epitopes are required to achieve a theoretical protection level of at least 90% (Table 2). The different numbers of required epitopes reflect the relative amounts of HLA class I polymorphism observed in the different ethnic groups and presentation of a peptide by multiple HLA class I molecules. To date, HIV peptides have been associated only with HLA restriction elements that are infrequent in some populations. As more data are accumulated for other epitopes, some that are associated with higher frequency restriction elements may be identified.

A comparison between the individual and combined populations (Table 2) demonstrates that relatively little is gained by including epitopes that are associated with low frequency alleles. The proportion of individuals protected approaches 100% asymptotically so that even adding on epitopes associated with high frequency alleles adds little to the proportion as this level is approached. This is illustrated by the North American Indians where including 6 more epitopes associated with 5 very low frequency alleles and one intermediate frequency allele in the combined theoretical vaccine adds only 3.0% protection.

U.S. Pat. No. 5,993,819 (the contents of which is incorporated herein by reference) also includes a description of the steps involved in the development of an HLA-based HIV vaccine. In Table XXVI of that patent, the following vaccine formula is provided which is equally applicable here:

Th₁,X₁, Th₂,X₂, Th₃,X₃, … Thₙ,Xₙ

where Th-immunodominant T helper epitopes and X=MHC Class I CTL epitope. In the context of a preferred embodiment of the invention, Table 3 provides specific Th-X peptides (see vaccines 6, 8 and 10, particularly vaccines 6 and 8) that can be admixed, formulated with a pharmaceutically acceptable carrier, and adjuvant, as appropriate, and administered to a patient in order to effect immunization. The optimum amount of each peptide to be included in the vaccine and the optimum dosing regimen can be determined by one skilled in the art without undue experimentation.

As an alternative to using mixtures of individual Th-X peptides, the vaccine of the presently preferred embodiment can also take the form of a linear array of Th-X epitopes (see the linear arrays of MVA 6-10 in Table 4, particularly MVA 6 and MVA 8), preferably, expressed in a modified Vaccinia ankara (Zentralbl. Bakteriol. 167:375-390 (1978); Nature Med. 4:397-402 (1988)) or other live vector such as an adenoviral vector or a canary pox vector (Weinhold et al, Proc. Natl. Acad. Sci. 94:1396-1401 (1997)). Upon expression with HIV gag p55, pseudovirions (particles) are produced (see, for example, the linear arrays of MVA 7 and 9 in Table 4). Standard procedures can be used to formulate the vaccine (e.g., with a carrier and, as appropriate, with an adjuvant) and optimum dosing regimes can be determined by one skilled in the art without undue experimentation.

In a further embodiment, the vaccine of the present invention includes MHC Class I restricted cytotoxic T lymphocytes (CTL) epitopes from HIV p17 and p24 gag regions. Known HIV CTL epitopes and their MHC restricting elements are listed in “HIV Molecular Immunology Database, 1999” (Korber, B T M, Brander, C., Haynes, B. F. et al Editors, Published by the Theoretical Biology and Biophysics Group T-10, Mail Stop K710 Los Alamos National Laboratory, Los Alamos, N. Mex. 87545). The CTL regions designated CT-I, CT-K, CT-L and CT-M are selected for Vaccine 11 in Table 3. The full peptide has been designed to have at the N-terminus of the epitope the optimal Th determinant, ThA E9V from HIV gp120 C4 region. The restricting elements predicted to respond to these peptides are listed to the right in Table 3. Thus, a practical HIV gag CTL immunogen is set forth in Table 6, with A-Th/A-CTL and B-Th/B-CTL peptides mixed with the peptides in Vaccine 11. The 25 HLA Class I molecules predicted to recognize the peptides in the mixture of peptides in Table 6 are listed at the bottom of the table.

Complex immunogens made up of CTL sequences, for example, from the Los Alamos Database (Korber, B T M, Brander, C., Haynes, B. F. et al Editors, Published by the Theoretical Biology and Biophysics Group T-10, Mail Stop K710 Los Alamos National Laboratory, Los Alamos, N. Mex. 87545) can be prepared by adding to the sequences in Table 6, new sequences from CTL epitopes in envelope, rev, nef, tat, pol and other regions of the HIV genome. These sequences can be formulated with T helper sequences as above in Table 6 (generic Th-X1, Th-X2…Th-Xn), or can be delivered in shorter sequences of X1, X2, …Xn, with T cell help being delivered by an appropriate adjuvant. In these generic designs, Th represents a helper T cell epitope, and X represents a HLA I restricted CTL epitope.

At each CTL sequence, there are many variants that can be included in the peptide mix in the above vaccine designs, in order to provide CTL that attack a sufficient number of HIV variants to prevent infection or to control infection. Variants are listed for each HIV Clade in the Los Alamos database for HIV sequences, “Human Retroviruses and AIDS”, Kuiken, C, Foley, B et al Editors, Published by the Theoretical Biology and Biophysics Group T-10, Mail Stop K710 Los Alamos National Laboratory, Los Alamos, N. Mex. 87545.

Since different geographic locations around the world have different HIV Clades infecting patient cohorts, the above peptide design can be modified to be appropriate for the Clade or Clades of HIV that are relevant for a particular geographic region. For example, the Los Alamos
Database of HIV Sequences has a listing of sequences by country and by clade. Therefore, to design a CTL vaccine for Zambian in Sub-Saharan Africa, the principles and general CTL epitope design described as above can be employed but using the most common or consensus sequences of the Clades and isolates in the data base from Zambia. This general strategy applies to design of CTL immunogens for any geographic region of the world.

[0033] Peptides have the greatest use in focusing the immune response on many dominant and subdominant CTL epitopes of HIV, but may benefit from a prime from another type of immunogen. Thus, the sequences described above and given in Tables 3 and 6, as well as Zambian sequences and or sequences of epitopes from rev, nef, tat, pol or env, can also be constructed in linear arrays of CTL epitopes with or without T helper determinants, for example, in either plasmid DNA constructs or in live vector constructs such as Modified Vaccinia Ankara or in mycobacteria tuberculosis strains that are attenuated, such as BCG (Jacobs et al, Nature Medicine 2:234 (1996)). These DNA or live vectors with linear arrays of CTL epitopes can be used as either primes or boosts of peptides or of each other to optimally give CTL anti-HIV responses.

[0034] It will be appreciated that this embodiment of the invention includes not only the specific Th-x peptides, and derivatives thereof (e.g. as shown in MVA 7 and MVA 9 in Table 4), shown, for example, in Tables 3 and 4, but also includes variants of the indicated peptides as well, particularly variants of the CTL epitopes shown. The mixture or linear array of Th-X peptides can be used alone or as one component of a multi-component vaccine. It will also be appreciated that the peptides of the invention can be synthesized using standard techniques. It will also be appreciated that the vaccine of the present invention can take the form of a DNA vaccine the expression of which in vivo results in the expression of the peptides, or linear arrays of same, described above.

[0035] Suitable routes of administration of the present vaccine include systemic (e.g. intramuscular or subcutaneous). Alternative routes can be used when an immune response is sought in a mucosal immune system (e.g., intranasal). Appropriate routes and modes of administration can be selected depending, for example, on whether the vaccine is a peptide or DNA vaccine or combination thereof.

[0036] Certain aspects of the present invention are described in greater detail in the Example that follows.

**EXAMPLE 1**

Studies of Th-CTL Mutivalent in HLA B7+ Humans

[0037] Immunogenicity and Safety of the C4-V3 Th-CTL Polyclonal Immunogen in HIV Seropositive Patients with CD4+ T Cell Counts<500/mm3 (DAIR010). The DAIR010 human trial of the C4-V3 PV immunogen has been completed (Bartlett et al, AIDS Res. Hum. Retro. 12:1291-1300 (1998)). The immunogen was a 4 Th-CTL peptides with the Th epitope the same in each peptide and the CTL peptide was four variants of a B7-restricted env CTL epitope (Haynes, Res. Human Retro. 11:211-221 (1995), Beddows et al. J. Gen. Virol. 79:77-82 (1998), Table 5). Ten HIV-infected, HLA B7-positive patients with CD4+-T cells>500/mm3 were enrolled. Eight patients received 2 mg of C4-V3 polyclonal immunogen (ie, 500 μg of each peptide) emulsified in incomplete Freund’s adjuvant (Seppic ISA51) IM X5 over 24 weeks, and 2 controls received ISA51 IM alone. Vaccine recipients had excellent boosts of Th proliferative levels and neutralizing antibody levels to TCLA/HIV (Bartlett et al, AIDS Res. Hum. Retro. 12:1291-1300 (1998)). However, in the setting of HIV infection, PBMC suspensions of immunized B7+ subjects had minimal direct CTL activity to the B7-restricted env CTL epitope in the immunogen to peptide coated targets or to vaccinia infected targets (i.e. the B7 gp120 CTL epitope was non-dominant in the setting of HIV infection) (Bartlett et al, AIDS Res. Hum. Retro. 12:1291-1300 (1998)).

[0038] AVEG020 Trial of Th-CTL C4-V3 Peptides in Seronegative Subjects. In conjunction with NAID, DAIDS, DATRI and WLVIP, AVEGO20 “Phase 1 Safety and Immunogenicity Trial of C4-V3 Peptide Immunogen in HIV Seronegative Subjects” was carried out at Vanderbilt, Rochester, and Seattle as a multicenter trial (AVEG020 Doses: High Dose=4 mg total dose, 1 mg of each peptide per dose; Low Dose=1 mg total dose, 250 μg of each peptide per dose).

[0039] Studies were made of 13 subjects (9, B7- and 4 B7+) after two immunizations 250 μg of each peptide variant. Of 9 HLA B7-subjects, 0/9 had PB CTL activity to any of the peptide variants of the B7-restricted gp120 env CTL epitope in the immunogen (FIGS. 1B and 1D). In contrast, 2/4 HLA B7+subjects had high levels of CTL activity to the B7 epitope that was mediated by CD8+ T cells and was MHC restricted after only two immunizations (FIGS. 1A and 1C). These data provided direct evidence that Th-CTL immunogens, when formulated in potent adjuvants, could induce MHC Class I-restricted CAIT in humans. Whereas one subject responded to one of the 4 B7 epitope variants, the other subject (FIG. 1A) responded to 3 of the 4 CTL variants. These data demonstrated that a human host could respond to more than one CTL epitope variant in an immunogen, and indicated that epitope-based immunizations could be used to induce MHC Class I-restricted CD8+ CTL responses to CTL epitopes and to their variants.

[0040] All documents cited above are hereby incorporated in their entirety by reference.

[0041] One skilled in the art will appreciate from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention.
### TABLE 1-continued

Frequencies of HLA Class I Alleles That are Known to Serve as HIV CTL Restriction Elements in Four Populations

<table>
<thead>
<tr>
<th>HLA Alleles</th>
<th>African Americans</th>
<th>USA Caucasians</th>
<th>North American Indians</th>
<th>Thais</th>
</tr>
</thead>
<tbody>
<tr>
<td>A31</td>
<td>1.7</td>
<td>2.0</td>
<td>27.5</td>
<td>1.7</td>
</tr>
<tr>
<td>A32</td>
<td>1.0</td>
<td>5.1</td>
<td>2.0</td>
<td>0.2</td>
</tr>
<tr>
<td>A33</td>
<td>0.1</td>
<td>1.0</td>
<td>1.0</td>
<td>13.6</td>
</tr>
<tr>
<td>B7</td>
<td>8.3</td>
<td>10.0</td>
<td>3.9</td>
<td>2.7</td>
</tr>
<tr>
<td>B8</td>
<td>3.2</td>
<td>10.0</td>
<td>5.6</td>
<td>0.2</td>
</tr>
<tr>
<td>B12 (44)</td>
<td>6.2</td>
<td>10.4</td>
<td>3.9</td>
<td>5.4</td>
</tr>
<tr>
<td>B13</td>
<td>0.9</td>
<td>3.0</td>
<td>1.0</td>
<td>9.3</td>
</tr>
<tr>
<td>B14</td>
<td>3.0</td>
<td>4.1</td>
<td>2.9</td>
<td>0.4</td>
</tr>
<tr>
<td>B17</td>
<td>10.9</td>
<td>4.9</td>
<td>1.0</td>
<td>8.1</td>
</tr>
<tr>
<td>B18</td>
<td>3.3</td>
<td>4.9</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>B27</td>
<td>1.6</td>
<td>4.1</td>
<td>2.9</td>
<td>6.0</td>
</tr>
<tr>
<td>B35</td>
<td>7.7</td>
<td>8.5</td>
<td>18.6</td>
<td>2.5</td>
</tr>
<tr>
<td>B37</td>
<td>0.9</td>
<td>2.2</td>
<td>0.0</td>
<td>1.4</td>
</tr>
<tr>
<td>B52</td>
<td>1.1</td>
<td>1.2</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>B53</td>
<td>12.8</td>
<td>0.8</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>B57</td>
<td>4.2</td>
<td>3.9</td>
<td>1.0</td>
<td>5.2</td>
</tr>
<tr>
<td>B60</td>
<td>1.3</td>
<td>4.5</td>
<td>2.9</td>
<td>8.3</td>
</tr>
<tr>
<td>B62</td>
<td>1.4</td>
<td>5.5</td>
<td>4.9</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*Frequencies for HLA-A and HLA-B alleles are taken from HLA 1991 [21]. HLA-C for African Americans and USA Caucasians are taken from Histocompatibility Testing 1984 [19]. HLA-C for North American Indians from Williams and McAuley, 1992 [22] and HLA-C for Thais from the Proceedings of the Second Asia and Oceana Histocompatibility Workshop Conference [23].

### TABLE 2

Proportion of each of the four populations that would be predicted to present peptides to the immune system

<table>
<thead>
<tr>
<th>Population</th>
<th>HLA Residues</th>
<th>HIV Epitope</th>
<th>Elements Chosen</th>
<th>Protein Location Epitope</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) African Americans</td>
<td>A2, A3, A11, B35 nef</td>
<td>73-82</td>
<td>QVPLARNMTYK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A28, B14</td>
<td>gp41</td>
<td>584-592</td>
<td>VELYLDQQL</td>
</tr>
<tr>
<td>A30, B8</td>
<td>gp41</td>
<td>844-863</td>
<td>RRIQQGLARALL</td>
<td></td>
</tr>
<tr>
<td>B17, B37</td>
<td>nef</td>
<td>117-128</td>
<td>TQYFPQKQVYK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gp120</td>
<td>576-383</td>
<td>(6) PFGGGEFP</td>
<td></td>
</tr>
<tr>
<td>(Proportion of African Americans expected to present these 5 epitopes is 92.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) USA Caucasians</td>
<td>A2, A3, A11, B35 nef</td>
<td>73-82</td>
<td>QVPLARNMTYK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A30, B8</td>
<td>gp41</td>
<td>844-863</td>
<td>RRIQQGLARALL</td>
</tr>
<tr>
<td>B7</td>
<td>gp120</td>
<td>302-312*</td>
<td>RPNNRTKREI</td>
<td></td>
</tr>
<tr>
<td>B12</td>
<td>nef</td>
<td>126-130*</td>
<td>NTVFPQGVRPELT</td>
<td></td>
</tr>
<tr>
<td>(Proportion of USA Caucasians expected to present these 4 epitopes is 90.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) North American Indians</td>
<td>A2, A3, A11, B35 nef</td>
<td>73-82</td>
<td>QVPLARNMTYK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A54</td>
<td>gp41</td>
<td>584-591*</td>
<td>YLKDQQL</td>
</tr>
<tr>
<td></td>
<td>nef</td>
<td>120-144*</td>
<td>YFFQMQYTFSPGQYIRLYPLRTGFQCYK</td>
<td></td>
</tr>
<tr>
<td>A31</td>
<td>gp41</td>
<td>770-780</td>
<td>RLADLLLIVTR</td>
<td></td>
</tr>
<tr>
<td>(Proportion of North American Indians expected to present these 3 epitopes is 96.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Thais</td>
<td>A2, A3, A11, B35 nef</td>
<td>73-82</td>
<td>QVPLARNMTYK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A24</td>
<td>gp41</td>
<td>584-591*</td>
<td>YLKDQQL</td>
</tr>
<tr>
<td></td>
<td>nef</td>
<td>120-144*</td>
<td>YFFQMQYTFSPGQYIRLYPLRTGFQCYK</td>
<td></td>
</tr>
<tr>
<td>(Proportion of Thais expected to present these 2 epitopes is 93.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>e) African Americans</td>
<td>A2, A3, A11, B35 nef</td>
<td>73-82</td>
<td>QVPLARNMTYK</td>
<td></td>
</tr>
<tr>
<td>USA Caucasians</td>
<td>A26, B14</td>
<td>gp41</td>
<td>584-592</td>
<td>VELYLDQQL</td>
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<tr>
<td>North American</td>
<td>A30, B8</td>
<td>gp41</td>
<td>844-863</td>
<td>RRIQQGLARALL</td>
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<tr>
<td>Thais</td>
<td>B17, B37</td>
<td>gp120</td>
<td>376-383</td>
<td>(5) FPGGGEFP</td>
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<td></td>
<td>B7</td>
<td>gp120</td>
<td>302-312*</td>
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<td>nef</td>
<td>126-130*</td>
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<td></td>
<td>B12</td>
<td>p24</td>
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<td>A31</td>
<td>gp41</td>
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[0042]
TABLE 2-continued

<table>
<thead>
<tr>
<th>HLA Resolution</th>
<th>HIV Epitope</th>
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<tr>
<td>Population</td>
<td>Elements Chosen</td>
</tr>
<tr>
<td>A24</td>
<td>gp41</td>
</tr>
</tbody>
</table>

(Proportions of African Americans, USA Caucasians, North American Indians, and Those expecting to present these 9 epitopes are 95.4%, 97.5%, 99.4%, and 97.2%, respectively)

*The criteria upon which choices among peptides should be made are not yet known. It may be important to choose peptides that have been reported to be immunogenic in non-progressors to AIDS or that have been reported to induce immunodominant anti-HIV T-cell responses.*

[0043]

TABLE 3

<table>
<thead>
<tr>
<th>Vaccine number</th>
<th>Name of Peptides</th>
<th>Species on which to be studied</th>
<th>Amino acid sequence</th>
<th>Restricting elements for CTL epitope</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mouse HIV-1 Th-CTL epitopes</td>
<td>Th - CTL</td>
<td>A-Th/A-CTL</td>
<td>HAGPIAPQOMNEPRG-KQIQINMQEGKAYMA</td>
<td>H-2 2nd</td>
</tr>
<tr>
<td>2. Mouse HIV-1 Th-CTL epitopes</td>
<td>Th - CTL</td>
<td>B-Th/B-CTL</td>
<td>ENQYLANWPAHEGIO-RYAVPISQDSQ</td>
<td>H-2 K 2nd</td>
</tr>
<tr>
<td>3. Macaque SIV/HIV-1 Th-CTL epitopes</td>
<td>Th - CTL</td>
<td>C-Th/C-CTL</td>
<td>QLFIHFPRLGHSK-DISVEIVQAOARIR</td>
<td>H-2 2nd (D')</td>
</tr>
<tr>
<td>5. Macaque SIV/HIV-1 Th-CTL plo epitope variants</td>
<td>Th - CTL</td>
<td>Th2/Th2/SIV Gag</td>
<td>EELXKIVKVEFLGAVPAKTA-CFPYDINQM</td>
<td>Mamu-A*01</td>
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<tr>
<td>8. Human HIV-1 Th-dominant/ subdominant CTL epitopes</td>
<td>Th - CTL</td>
<td>A-Th/A-CTL</td>
<td>KQIINMQEGKAYMA-KAPSVPIVMF</td>
<td>HLA B57, B58</td>
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<tr>
<td>9. Human HIV-1 Th-dominant/ subdominant CTL epitopes</td>
<td>Th - CTL</td>
<td>B-Th/B-CTL</td>
<td>YKKWIIILGKIV/RMS-YFPFPGVEYERPM</td>
<td>HLA B35, B8, B27, A2, A3, A3L</td>
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<tr>
<td>10. Human HIV-1 Th-CTL p17 epitope (2A Variants)</td>
<td>Th - CTL</td>
<td>C-Th/C-CTL</td>
<td>DREVQVYQAVRAIR-KWMEILNK</td>
<td>HLA B27</td>
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</table>
TABLE 3-continued

<table>
<thead>
<tr>
<th>Vaccine number</th>
<th>Name of Peptides</th>
<th>Species on which to be studied</th>
<th>Amino acid sequence</th>
<th>Restricting elements for CTL epitope</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Human HIV-1 Th-CTL overlapping epitopes</td>
<td>A*+Th/1&lt;CTL</td>
<td>Th&lt;CTL</td>
<td>EQLMNQVVGKAMYA-GQHVQALSPHTLMAYNF KVV</td>
<td>A2, A202, A5, A7, B14, B57, B5701, B5801, B02, Cw3</td>
</tr>
<tr>
<td></td>
<td>A*+Th/R&lt;CTL</td>
<td></td>
<td>EQLMNQVVGKAMYA-AGTPQDLSTHLNVTGOGH QAMQMLKETRMDAAEW</td>
<td>A2, A25, A26, B7, B12, B14, B1402, B27, B39, B52, B53, B57, B58, B8101, Cw8, Cw102</td>
</tr>
<tr>
<td></td>
<td>A*+Th/L&lt;CTL</td>
<td></td>
<td>EQLMNQVVGKAMYA-GPKFPFETYDVDFYTIT LIQFAQGQYKHM</td>
<td>A2, A202, A5, A24, A2402, A25, A26, A33, B7, B8, B12, B14, B35, B39, B44, B52, B53862, Cw3, Cw6, Cw0041</td>
</tr>
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A*+Th = C4E8V

[0044]

TABLE 4

Linear Array of Th-CTL Epitopes To Be Expressed in Modified Vaccinia Ankara

MVA-1) HIV-1 mouse Th-CTL epitopes in


HA沟APAQPQMRFPSG→QQHNMQWGGHGKAMYA→KEKVYVLAIVVPARRAGS→MYAPIPGGQH

C-Thpe44(4-25) → C-CTLgp120(12-24) → C-ThpeRT(12-24) → C-CTLgp120(12-24)

QLHFHRGCGRHR→DRVEVQVAYRIR→EQMHEEDSLWDQSL→RPHGFAFYTTKN

MVA-2) p55/pag + the same HIV-1 mouse Th-CTL epitopes in MVA-1

MVA-3) HIV-1/SIV Th-CTL epitopes in

Th2DRB*505 + C-CTLgp120(12-24) → CTLMGag/p11cA

EFLYKXVVKIEPIEGVTAPK→CTPYDNNML→VSTVQCHD0PVSTQGML→CTPYDNNML

CTLP314 → CTLMGag/p11cA → CTE4P12 → CTLMGag/p11cA

STSRGK vidaFAYFKR→CTPYDNNML→EAYFFYKDLHPIDNTDTSY→CTPYDNNML

CTLP314 → CTLMGag/p11cA

MVA-4) p55/pag + the same HIV-1/SIV Th-CTL epitopes in MVA-3

MVA-5) SIV Th-CTL p11c epitope variants in
TABLE 4-continued

Linear Array of Th-CTL Epitopes To Be Expressed in Modified Vaccinia Ankara

<table>
<thead>
<tr>
<th>Peptide</th>
<th>C4-V3 Region</th>
<th>gp120 C4 Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4-V3MN</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 C4 Region</td>
</tr>
<tr>
<td>C4-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
</tr>
<tr>
<td>C4-V3EYV1</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
</tr>
<tr>
<td>C4-V3CanOA</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
</tr>
<tr>
<td>C4-V3G-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
</tr>
</tbody>
</table>

MVA-6) HIV-1 human Th-CTL overlapping epitopes in

RESTRICTING ELEMENTS FOR CTL: epitopes
A-CTL epitope = HLA B7/888; B-CTL epitope = HLA B35/B8/B27/A33/Bw62/B52.
MVA-7) p55 gag + the same HIV-1 human Th-CTL overlapping epitopes in MVA-6
MVA-8) HIV-1 Th dominant/subdominant CTL epitopes in

<table>
<thead>
<tr>
<th>Peptide</th>
<th>C4-V3 Region</th>
<th>gp120 C4 Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4-V3MN</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 C4 Region</td>
</tr>
<tr>
<td>C4-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
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<tr>
<td>C4-V3EYV1</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
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<tr>
<td>C4-V3CanOA</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
</tr>
<tr>
<td>C4-V3G-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
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TABLE 5-continued

HIV Polyvalent C4-V3 Peptides Studied in Guinea Pigs, Primates Or In Humans

<table>
<thead>
<tr>
<th>Peptide</th>
<th>gp120 C4 Region</th>
<th>gp120 V3 Region</th>
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<tbody>
<tr>
<td>C4-V3MN</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 C4 Region</td>
</tr>
<tr>
<td>C4-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
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<tr>
<td>C4-V3EYV1</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
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<tr>
<td>C4-V3CanOA</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
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<tr>
<td>C4-V3G-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
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</table>

<table>
<thead>
<tr>
<th>Peptide</th>
<th>gp120 C4 Region</th>
<th>gp120 V3 Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4-V3MN</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 C4 Region</td>
</tr>
<tr>
<td>C4-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
</tr>
<tr>
<td>C4-V3EYV1</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
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<tr>
<td>C4-V3CanOA</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
</tr>
<tr>
<td>C4-V3G-V3RF</td>
<td>KQ11NMQVEVGMATQRPFRNENRKNLH3GPPGVRFTYTK</td>
<td>GP120 V3 Region</td>
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Sequences from the Los Alamos Database.
### TABLE 6

<table>
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<th>Vaccine number</th>
<th>Name of Peptides</th>
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<tbody>
<tr>
<td>6</td>
<td>A-Th/A-CTL</td>
<td>KQIIIMMQQVGMAYAKPFSPEVIHM</td>
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<tr>
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<td>B-Th/B-CTL</td>
<td>YKSMIIQLNKIVSMTS- NPPVPGEIYKSWIILGLNIVRMSTPSI</td>
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<tr>
<td>11</td>
<td>A*-Th/J-CTL</td>
<td>KQIIIMMQQVGMAYA- GQMVGQAISFRTLMNNKVV</td>
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<tr>
<td>11</td>
<td>A*-Th/K-CTL</td>
<td>KQIIIMMQQVGMAYA- ATPQGLNPHMTVQGHHQAMQNLKSLINEEAEM</td>
</tr>
<tr>
<td>11</td>
<td>A-Th/L-CTL</td>
<td>KQIIIMMQQVGMAYA- GPKEFFPVQVDFYFTLSAEQASQVEVKNMT</td>
</tr>
</tbody>
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**A*-Th = C418PV**

Summary of restricting elements for CTL epitopes in Vaccines A, B, J, K, L and M

A: A1, A2 (O1, O2), O1, A3, A3.1, A5, A11, A23, A24 (O2), A25, A26 and A33.
B: B7, B8, B12, B14 (O2), B27 (O5), B35, B39, B42, B44, B52, B53, B57 (O1), B58 (O1) B62 (w62), B70 and B71.
C: Cw3, Cw6, Cw0401 and Cw8.

HIV Th/CTL vaccine.ABULMN

---

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<213> ORGANISM: Human immunodeficiency virus

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<210> SEQ ID NO 2
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<406> SEQUENCE: 6

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<211> LENGTH: 16

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<213> ORGANISM: Human immunodeficiency virus

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  1  5  10

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<400> SEQUENCE: 9

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1   5

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Pro Leu Thr Phe Gly Thr Cys Tyr Lys 20   25

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1   5   10

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1   5

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1   5   10   15
Pro Leu Thr Phe Cys Gly Thr Cys Tyr Lys 20   25

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<213> ORGANISM: Murine sp.

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Gln Ile Ile Asn Met Trp Gin Glu Val Gly Lys Ala Met Tyr Ala
20 25 30

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<212> TYPE: PRT
<213> ORGANISM: Murine sp.

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Met Tyr Ala Pro Pro Ile Gly Gin Gin Ile
20 25

<210> SEQ ID NO 16
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1 5 10 15
Arg Val Ile Glu Val Val Gin Gin Gly Ala Tyr Arg Ala Ile Arg
20 25 30

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<213> ORGANISM: Murine sp.

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Glu Gin Met His Glu Asp Ile Ile Ser Leu Trp Asp Gin Ser Leu Arg
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Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Thr Thr Lys Asn
20 25 30

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<213> ORGANISM: Macaque sp.

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Pro Thr Lys Ala Cys Thr Pro Tyr Asp Ile Asn Gin Met
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Gln Leu Leu Leu Ser Thr Pro Pro Leu Val Arg Leu
20 25
Ser Thr Ser Ile Arg Gly Lys Val Glu Lys Tyr Ala Phe Phe Tyr
  1    5    10   15
Lys Leu Asp Ile Tyr Ala Pro Ile Ser Gly Gln Ile
  20   25

Val Ser Thr Val Glu Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
  1    5    10   15
Gln Leu Leu Leu Cys Thr Pro Tyr Asp Tyr Asn Gln Met Leu
  20   25   30

Ser Thr Ser Ile Arg Gly Lys Val Glu Lys Tyr Ala Phe Phe Tyr
  1    5    10   15
Lys Leu Asp Ile Cys Thr Pro Tyr Asp Ala Asn Gln Met Leu
  20   25   30

Glu Tyr Ala Phe Phe Tyr Lys Leu Asp Ile Ile Pro Ile Asp Asn Asp
  1    5    10   15
Thr Thr Ser Tyr Cys Thr Pro Tyr Asp Asp Asn Gln Met Leu
  20   25   30

Arg Glu Gin Phe Gly Asn Asn Lys Thr Ile Ile Phe Lys Gin Ser Ser
  1    5    10   15
Gly Gly Asp Pro Glu Cys Thr Pro Tyr Asp Lys Asn Gln Met Leu
  20   25   30
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Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala
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Lys Ala Phe Ser Pro Glu Val Ile Pro Met Phe
20 25

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Ser Asn Pro Pro Ile Val Gly Ile Tyr Lys Arg Trp Ile Ile
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35 40 45

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<213> ORGANISM: Homo sapiens

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Gly Phe Pro Val Arg Pro Gly Val Val Pro Leu Arg Pro Met Thr Tyr Lys
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<213> ORGANISM: Homo sapiens

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Val Tyr His Thr Glu Gly Phe Phe Pro Asp Trp Gln Asn Tyr Thr Pro
20 25 30

<210> SEQ ID NO 29
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<213> ORGANISM: Homo sapiens

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1 5 10 15
Ser Leu Tyr Asn Thr Val Ala Thr Leu
20 25

<210> SEQ ID NO 30
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30
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<213> ORGANISM: Homo sapiens
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Leu Tyr Asn Thr Val Ala Val Leu
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Leu Phe Asn Leu Leu Ala Val Leu
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<210> SEQ ID NO 39
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20  25  30
Val Lys Val Val
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1  5  10  15
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Glu Trp
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Gly Pro Lys Glu Pro Phe Arg Asp Tyr Val Asp Arg Phe Tyr Lys Thr
  20  25  30
Leu Arg Ala Glu Gln Ala Ser Gin Glu Val Lys Asn Trp Met Thr
  35  40  45

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  20  25  30
Ile Val Trp Gly Ser Gin Leu Arg Ser Leu Tyr Asn Thr Val Ala
  35  40  45
Thr Leu Tyr Cys Val His Gin Arg Ile
  50  55

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His Ala Gly Pro Ile Ala Pro Gly Gin Met Arg Glu Pro Arg Gly
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<210> SEQ ID NO 44
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<212> TYPE: PRT
<213> ORGANISM: Murine sp.

<400> SEQUENCE: 44

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  1  5  10  15

<210> SEQ ID NO 45
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<212> TYPE: PRT
<213> ORGANISM: Murine sp.

<400> SEQUENCE: 45

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<212> TYPE: PRT
<213> ORGANISM: Murine sp.

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Gln Leu Leu Phe Ile His Phe Arg Ile Gly Cys Arg His Ser Arg
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<213> ORGANISM: Murine sp.

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1  5 10 15

Pro Thr Lys Ala
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Cys Thr Pro Tyr Asp Ile Asn Gln Met
1  5
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Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
  1       5       10    15
Gln Leu Leu Leu
  20

Ser Thr Pro Pro Leu Val Arg Leu
  1       5

Ser Thr Ser Ile Arg Gly Lys Val Gln Lys Glu Tyr Ala Phe Phe Tyr
  1       5       10    15
Lys Leu Asp Ile
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Tyr Ala Pro Pro Ile Ser Gly Gln Ile
  1       5

Glu Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala
  1       5       10    15
Pro Thr Lys Ala
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Cys Thr Pro Tyr Asp Ile Asn Gln Met Leu
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Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr
1 5 10 15
Gln Leu Leu Leu Leu
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Cys Thr Pro Tyr Asp Tyr Asn Gln Met Leu
1 5 10

Ser Thr Ser Ile Arg Gly Lys Val Gln Lys Glu Tyr Ala Phe Phe Tyr
1 5 10 15
Lys Leu Asp Ile Leu
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Cys Thr Pro Tyr Asp Ala Asn Gln Met Leu
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Glu Tyr Ala Phe Phe Tyr Lys Leu Asp Ile Ile Pro Ile Asp Asn Asp
1 5 10 15
Thr Thr Ser Tyr
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Arg Glu Gln Phe Gly Asn Asn Lys Thr Ile Ile Phe Lys Gln Ser Ser  
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Gly Gly Asp Pro Glu  
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Cys Thr Pro Tyr Asp Lys Asn Gln Met Leu  
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Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala  
   1 5 10 15  

Lys Ala Phe Ser Pro Glu Val Ile Pro Met Phe  
   1 5 10  

Tyr Lys Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr  
   1 5 10 15  
Ser  

Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys Arg Trp Ile Ile Leu  
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Gly Leu Asn Lys Ile Val Arg Met Tyr Ser Pro Thr Ser Ile  
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Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr
1 5 10 15

Lys

Ala Ser Leu Trp Asn Trp Phe Asn Ile Thr Asn Trp Leu Trp Tyr
1 5 10 15

Trp Val Tyr His Thr Gln Gly Phe Phe Pro Asp Trp Gln Asn Tyr Thr
1 5 10 15

Pro

Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala
1 5 10 15

Ser Leu Tyr Asn Thr Val Ala Thr Leu
1 5
Tyr Lys Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr
   1     5     10     15

Ser

Lys Ile Arg Leu Arg Pro Gly Gly Lys
   1     5

Asp Arg Val Ile Glu Val Val Gln Gly Ala Tyr Arg Ala Ile Arg
   1     5     10     15

Lys Arg Trp Ile Ile Leu Gly Leu Asn Lys
   1     5     10

Ala Ser Leu Trp Asn Thr Asn Thr Asn Trp Leu Trp Tyr
   1     5     10     15
Th-dominant/subdominant CTL epitopes in MVA.

Gly Gly Lys Lys Tyr Lys Leu
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SEQ ID NO 83
LENGTH: 15
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: HIV-1 Th-dominant/subdominant CTL epitopes in MVA.

Met Arg Glu Pro Arg Gly Ser Lys Ile Ala Gly Thr Thr Ser Thr
1 5 10 15

SEQ ID NO 84
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: HIV-1 Th-dominant/subdominant CTL epitopes in MVA.

Glu Arg Tyr Leu Lys Asp Gln Gln Leu
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SEQ ID NO 85
LENGTH: 17
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: HIV-1 Th-CTL A2 p17 epitope (A2 Variants) in MVA

Tyr Lys Arg Trp Ile Ile Leu Gly Leu Leu Asn Lys Ile Val Arg Met Tyr
1 5 10 15

SEQ ID NO 86
LENGTH: 9
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: HIV-1 Th-CTL A2 p17 epitope (A2 Variants) in MVA

Ser Leu Tyr Asn Thr Val Ala Thr Leu
1 5

SEQ ID NO 87
LENGTH: 15
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Description of Artificial Sequence: HIV-1 Th-CTL A2 p17 epitope (A2 Variants) in MVA

SEQ ID NO 87
Asp Arg Val Ile Glu Val Val Gln Gly Ala Tyr Arg Ala Ile Arg
1 5 10 15

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Ser Leu Phe Asn Thr Val Ala Thr Leu
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1 5 10 15

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Ser Leu Tyr Asn Ala Val Ala Thr Leu
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Ala Ser Leu Trp Asn Trp Phe Asn Ile Thr Asn Trp Leu Trp Tyr
1 5 10 15

<210> SEQ ID NO 91
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<400> SEQUENCE: 91
Ser Leu Tyr Asn Thr Val Ala Val Leu
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<210> SEQ ID NO 93
<211> LENGTH: 15
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Net Arg Glu Pro Arg Gly Ser Lys Ile Ala Gly Thr Thr Ser Thr
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Ser Leu Phe Asn Leu Leu Ala Val Leu
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<210> SEQ ID NO: 95
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<210> SEQ ID NO: 96
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Arg Val Ile Tyr Ala Thr Gly
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Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala
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Thr Arg Pro His Asn Asn Thr Arg Lys Ser Ile His Met Gly Pro Gly
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Thr Arg Pro Asn Asn Thr Arg Lys Ser Ile Thr Lys Gly Pro Gly
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Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys Ala Met Tyr Ala
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What is claimed is:

1. A vaccine comprising a mixture or linear array of peptides, or variants thereof, selected from the peptides set forth in Table 3 and designated Th/A-CTL to Th/I-CTL and linear arrays by set forth in Table 4 and designated MVA 6-MVA 9.

2. A polypeptide having the formula

\[ \text{Th}_1 \text{X}_1 \text{Th}_2 \text{X}_2 \text{Th}_3 \text{X}_3 \ldots \text{Th}_n \text{X}_n \]

wherein Th is a immunodominant T helper epitope, X is an MHC Class I cytotoxic T cell epitope and N is any number.

3. The polypeptide according to claim 2 wherein N is 1 to 20.

4. The polypeptide according to claim 3 wherein N is 4 to 15.

5. The polypeptide according to claim 4 wherein N is 6 to 12.

6. A DNA sequence encoding the polypeptide of claim 2.

7. A composition comprising the polypeptide of claim 2 and a carrier.

8. A composition comprising the DNA sequence of claim 6 and a carrier.

* * * * *