Vaccinia and other viruses with available vaccines show marked homology with the HIV-1 envelope glycoprotein: The prospect of using existing vaccines to stem the AIDS pandemic

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Abstract
Cross-reactive immunity occurs when infection with or vaccination against one virus protects against another related family member. A search for homologues of the HIV-1 envelope glycoprotein revealed that it is composed of thousands of intercalating and overlapping viral matches of pentapeptide or longer gapped consensi, belonging to over 70% of the currently sequenced virome, infecting all kingdoms from bacteria to man. It was also highly homologous to proteins from the Visna/Maedi and other ovine viruses, while other proteins (nef/tat/gag/pol) were homologous to proteins from the equine infectious anaemia virus and HTLV-2/HTLV-3 viruses. This phenomenon suggests that horizontal gene transfer from coinfecting RNA and DNA viruses to retroviruses is extensive, providing a route for the subsequent insertion of non-retroviral genes into human and other genomes via retroviral integration. This homology includes all viruses for which vaccines already exist. Cross-reactive immunity may be operative in AIDS, as Vaccinia vaccination decreases viral replication in HIV-1 infected patients’ cells, for the CCR5 tropic form. Measles, Dengue virus, or GB virus C infections also decrease the HIV-1 viral load. A resumption of Vaccinia/smallpox vaccination might be expected to have a significant effect on the AIDS pandemic, and a careful study of the potential uses of other existing viral and bacterial vaccines merits close attention. This phenomenon may also be relevant to other recalcitrant viruses, bacteria, and parasites for which no vaccine exists and the armory of existing vaccines may have a role to play in diseases other than those for which they were designed.

Keywords: AIDS, HIV-1, smallpox, vaccine, vaccinia

Introduction
The birth of immunology, over 200 years ago, noted that smallpox could be prevented by inoculation with cowpox, a principle of immunity leading to the development of vaccines that have eliminated smallpox and which combat many other viral and bacterial diseases. Many viruses are however, recalcitrant to vaccination, particularly the AIDS virus, HIV-1. However it has recently been shown that Vaccinia virus vaccination reduces CCR5 tropic HIV-1 replication of the cells of infected patients. In HIV-1 infected patients the viral load has also been reported to be reduced in patients infected with measles or Dengue fever. The suppression of HIV-1 replication by measles infection is concurrent with intense immune activation. It has also been shown that GB virus type C infection prolongs the survival of HIV-1 infected patients and that this effect is related to antibodies raised to the GB virus envelope protein, that cross-react with HIV-1 particles. This latter effect suggests cross-reactive immunity. These apparent protective effects of other viral infections could also be related to a general activation of defense networks such as the protein kinase R or retinoic acid inducible gene (RIG-1) pathways leading to interferon production and the activation of antiviral signaling programs, although some viruses, including herpes simplex and influenza are able to subvert these and other pathways.
If cross-reactive immunity is also involved in such effects, one would expect a degree of homology between HIV-1 and other viral proteins, within antigenic regions. In an attempt to find homologous viruses that might serve as the cowpox equivalent to HIV-1, the HIV-1 envelope glycoprotein (env) was compared to all other viral proteomes. Short contiguous amino acid stretches (pentapeptides or longer gapped sequences) belonging to proteins from almost the entire current virome are encased within the env protein and include those for which vaccines are available. These could perhaps play a role in the development of cross-reactive immunity to HIV-1.

Methods

B-cell epitopes for the HIV-1 env glycoprotein (P04578: Human immunodeficiency virus type 1 group M subtype B (isolate HXB2)) were retrieved from the BepiPred server (http://www.cbs.dtu.dk/services/BepiPred/) and examples of immunogenic regions compared to all viral proteomes using the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) server (BLASTp). This env sequence was derived from the reference env gene in the NCBI gene database (NC_001802.1). To detect small intraprotein consensi, the E value was set to 100,000. HIV-1, HIV-2, and other immunodeficiency viruses (Bovine, Feline, and Simian, the HIV-like cancer virus or the Aids-associated retrovirus, and the Murine AIDS virus-related provirus) were eliminated from the search due to evident homology. A list of available viral vaccines was obtained from the Center for disease control website at http://www.cdc.gov/vaccines/vpd-vac/vaccines-list.htm. BLASTs against these specific viruses (Table 1) were also undertaken. The env protein epitopes registered in the Immune epitope database (http://www.immuneepitope.org) were also compared to these viruses. In some cases, the amino acid sequences of these env protein epitopes differed from that of the chosen example, due to viral strain differences. Viral matches (vatches) of five contiguous amino acids or more or longer gapped sequences were identified by eye and copied to a table in the appropriate position relative to the HIV-1 env amino acid sequence (Supplementary Table 1). The entire protein was not processed, but the many results illustrated the principles involved. To the author’s knowledge or ability, there is currently no way of automating this process (every single pentapeptide of the env glycoprotein tested shares similarity with several other viruses) and it is hoped that this illustration will stimulate work in this direction, which is also applicable to millions of vatches within the human proteome. Finally, the env protein from various HIV-1 strains was screened by BLAST analysis (BlastP) versus various Vaccinia viruses. The common peptides identified were analyzed for potential B cell immunogenicity using the Bepipred server. The server-set index of 0.35 was used as the immunogenicity index threshold.

Results

The env glycoprotein shows significant overall homology with proteins from four other viruses, the env proteins of the Caprine arthritis encephalitis virus (E=3e-12), the small ruminant lentivirus (E=6e-10), the visna/maedi virus (E=6e-06) and the ovine lentivirus (E=4e-04) (Figure 1). The HIV-1 nef protein showed significant overall homology with an ORF protein from HTLV-2 (E=2e-45), while the HIV-1 tat protein showed significant overall homology with the HTLV-3 tat protein (E=1e-35) (not shown). The HIV-1 gag protein is highly homologous to a protein from the puma lentivirus (E=1E-98) and to a gag protein from the equine infectious anaemia virus (E=3e-42) (Figure 1).

The results in relation to other viruses are shown in supplementary Table 1, where viral vatches are aligned with the env sequence, which is also characterized in relation to the B cell epitope index. Even though only 67% of the env protein was processed, HIV-1 vatches were observed in 1827 RNA and DNA viruses and phages, known to infect all kingdoms from bacteria to man. These were majoritarily species rather than strains. At the time of writing, there are 3753 reference sequences for 2565 viral genomes in the NCBI Entrez Genomes database, and the viruses containing HIV-1 env sequences account for 872% of the known current virome. Examples of such alignments, for viruses where vaccines are available, are shown in Table 1. All of these viruses contain HIV-1 vatches in both B cell epitope and non-epitope regions and within epitopes that have been experimentally verified.

A BLAST analysis of the env protein from several HIV-1 viral strains compared with Vaccinia viruses revealed a further layer of complexity. While certain identical Vaccinia/HIV-1 sequences were maintained across several HIV-1 viral strains, for example, the hexapeptides GAAGST or VVKIEP, these were often in differing positions of the env protein (e.g. GAAGST at positions 386, 510, 512, 524, 529, or 531). Otherwise, the profile of matching peptides derived from this sweep appears to be distinct for each strain of the HIV-1 virus. The viral matches shown in Tables 1 and 2 were predominantly pentapeptides, but longer contiguous or gapped sequences as well as frequent tetrapeptides were also observed (see supplementary Table 1).

Discussion

The close homology of the env nef, tat, and gag/pol proteins with caprine, ovine, visna/Maedi, equine, and small ruminant viruses and particularly with HTLV-2 and HTLV-3 is of evolutionary interest as it suggests a source of the AIDS virus and its relatives, prior to simian integration and passage to man. However this is not the subject of this article.

In terms of cross-reactive immunity, no vaccines for HTLV-2 or HTLV-3 yet exist, although interestingly,
Table 1. Examples of viral vatches within the HIV-1 envelope protein, for viruses where vaccines are available. (Continued)

| Virus and Alignments with the HIV-1 env protein | All are within a predicted B cell epitope region (or within an experimentally described IEDB epitope) |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------|
| Chickenpox (Human Herpesvirus 3)             | 73: A +PTDP+                                                                                     |
|                                              | 108: IIS W+                                                                                     |
|                                              | 121: KLTP LC TL                                                                                   |
|                                              | 142: SSSGR                                                                                   |
|                                              | 214: PIHY APA                                                                                   |
|                                              | 252: RP V +LL                                                                                   |
|                                              | 276: NFT NA                                                                                     |
|                                              | 305: KR R IG                                                                                    |
|                                              | 307: KRIH and KR RI                                                                             |
|                                              | 313: P RAF+ PGRA                                                                                |
|                                              | 413: TITLP                                                                                      |
|                                              | 500: KAKRRV                                                                                     |
|                                              | 502: KRRV                                                                                       |
|                                              | 573: GI QLQ                                                                                     |
|                                              | 574: IK QLQA                                                                                     |
|                                              | 690: GGLVG                                                                                      |
| Hepatitis A                                  | 38: VYYGV                                                                                       |
|                                              | 39: Y VPV WK                                                                                     |
| Hepatitis B                                  | 477: +NWRS+                                                                                     |
|                                              | 74: CVPTD                                                                                       |
|                                              | 75: VFTDP P                                                                                     |
|                                              | 492: EPLGV                                                                                      |
|                                              | 108: IS W SL and IISL                                                                            |
|                                              | 575: QL VLA                                                                                     |
|                                              | 608: VP NAS                                                                                     |
| Influenza A virus (many different strains)    | 32: DT+VHN                                                                                       |
|                                              | 42: VPVV                                                                                         |
|                                              | 108: ISLWDQ and IISL                                                                             |
|                                              | 110: ISLWDQ                                                                                     |
|                                              | 121: K T PL CV L                                                                                 |
|                                              | 124: PLCV L                                                                                     |
|                                              | 125: LCVT L                                                                                     |
|                                              | 131: CTDLK                                                                                      |
|                                              | 139: NTNSS                                                                                      |
|                                              | 142: SSSGR                                                                                      |
|                                              | 167: GKVQK                                                                                      |
|                                              | 205: CPKV S                                                                                     |
|                                              | 252: R IVSTQ and RPIV Q                                                                         |
|                                              | 254: IVSTQ                                                                                      |
|                                              | 263: GISA+                                                                                      |
|                                              | 294: INCTR                                                                                      |
|                                              | 298: RPNNN                                                                                      |
|                                              | 503: NNTRK and NNYN KRI I and NNYKR                                                           |
|                                              | 583: VE YL KD +L GC KL+C                                                                         |
|                                              | 584: E YLKD                                                                                      |
|                                              | 607: AV WNA and AV WN S                                                                         |
|                                              | 678: LW +I IF                                                                                    |
|                                              | 685: F1+V                                                                                       |
|                                              | 690: GGL GL                                                                                     |
|                                              | 708: VRQ YS LS                                                                                  |
|                                              | 712: YSPLS                                                                                      |
|                                              | 802: YW QEL                                                                                     |
|                                              | 803: W QELK                                                                                     |
| Japanese encephalitis virus                  | 59: KYT E                                                                                       |
|                                              | 110: SLWD                                                                                       |
|                                              | 240: T+STV                                                                                      |
|                                              | 241: NVSTV                                                                                      |
|                                              | 252: AGST+G A S TL R                                                                            |
|                                              | 576: L ARV Y L K                                                                                |
|                                              | 688: IVGL L I                                                                                   |
|                                              | 829: VIEVL R and VIE                                                                            |
|                                              | 830: IEVLQR                                                                                     |

(Continued)
Table 1. Examples of viral vatches within the HIV-1 envelope protein, for viruses where vaccines are available. (Continued)

| Viruses and Alignments with the HIV-1 envelope protein | (or within an experimentally described IEDB epitope) |
|--------------------------------------------------------|------------------------------------------------------|

| Measles virus (repeat motifs in Bold) | Mumps virus | Papillomavirus (several strains) | Poliovirus (1, 2 and 3) | Human Rotavirus A |
|--------------------------------------|-------------|---------------------------------|------------------------|--------------------|
| 55: ASDAKA 135: N NT SSS | 35: WVDQTY | 36: TVTVY | 252: RP+TQ | 121: KLCV |
| 109: ISL WD SL | 140: NT SSS | 58: AYDT+ | 255: VSTQ | 133: DLKND |
| 110: SLWD 254: I STQL | 60: AY+THN+ | 314: GRAYT | 208: ISF P+Y | 252: ARIVSTQ |
| 252: RPI SQQL 305: KRI IG | 70: ATAC | 336: AKW++ and AKNN | 303: YNKR | 307: KRIH and KRRI |
| 253: PI S QL 443: QS C NI | 74: CVPTDP| 529: TMGAA | 836: ACIPIRQG | 308: ARIH |
| 263: GSLA EE 493: PLGVA | 77: TDPNP | 531: GAAS+ | | |
| 304: NKRK 573: IK QLQA | 82: QE+VLV | | | |
| 308: RIH IGPG 577: QAR LA | 142: SSSGR | | | |
| 312: GPGR 688: IV GLV | 208: ISF+P | | | |
| 314: GRAF T 823: AEG RVI | 218: CAPA F | | | |
| 401: STEGS | 234: NGTGP | | | |
| 493: PLGVA | 238: PCNTNV | | | |
| 573: IKQL QA V | 239: CT N STVQC | | | |
| 581: LAVE LK | 240: TNVST | | | |
| 647: ESQ+QQ+ | 253: PI STQ | | | |
| 685: F+M LVGL | 264: SLAEE | | | |
| 688: IVGG V | 300: NNNTR | | | |
| 706: NRVQR | 301: NNTRK | | | |
| 707: RVROQ | 302: NTRKR | | | |
| 715: L+f+LPTR | 305: KRRI and KRKR+ | | | |
| 716: NRVQR | 349: LREQF | | | |
| 719: THLPT | 363: OSSGG | | | |
| 721: LPTPR | 364: SSGGD | | | |
| 732: GI EE+G+R | 401: STEGS | | | |
| DRDR | 406: NNTEG | | | |
| 801: +Y SQEL | 407: NTEGS | | | |
| 828: R EVVQ | 410: GSDTI | | | |
| | 413: TITTP | | | |
| | 440: SQQIR | | | |
| | 493: PLGVA | | | |
| | 497: APTKA | | | |
| | 500: KAKRR | | | |
| | 502: KRRVV | | | |
| | 570: VWGKIL+ | | | |
| | 574: KQLQ | | | |
| | 576: LQ VLA | | | |
| | 605: TTAVP | | | |
| | 633: REINY S | | | |
| | 635: I+NYTS | | | |
| | 644: SLIEES | | | |
| | 658: QELLE | | | |
| | 688: IVGG | | | |
| | 690: GG+VG | | | |
| | 721: LPTPR GP | | | |
| | 730: PEG++EGG | | | |
| | 731: EG+EEE | | | |
| | 734: EEEG E+R DS R | | | |
| | 799: LLWQEL | | | |
| | 806: ELKNS V | | | |
| | 807: LKNSA | | | |
| | 820: IAVAE D I E | | | |
| | 828: R IEVL | | | |

| Rabies virus | Rubella | Vaccinia virus or Vaccinia virus | Yellow fever virus |
|--------------|---------|----------------------------------|-------------------|
| 122: L LC+TL | 70: AT ACV | Tian Tan | 108: IIS DQ |
| 218: CAPA F | PTD | 34: K W+TV | 131: KC L D SSS |
| 226: PAG AI | 738: GGE DR | 35: LW YYG | 231: KTF GTG CT |
| 337: KWNH | 825: G DRV+ | 36: VT+Y GVPV | 259: LLLN E+ SVT N T I S E N CN PN R |
| 354: GNKNT | V Q | 37: T+YYG | 276: N D KTI V L T P |
| 584: ER+LK | 55: V L NAT I A | 57: DAKAY | 354: GNKNT |
| 687: MI GGL L | 82: Q VVLV | 417: PCRI I+ | |
| 800: LQ WSQ | 82: Q VVLV | 484: YK KVVK+ L AP KA V+ R+ R G | |
| 805: QELKKN | 108: II LW+ | 632: + EI NY S H | |

(Continued)
Table 1. Examples of viral vatches within the HIV-1 envelope protein, for viruses where vaccines are available. (Continued)

| Viruses and Alignments with the HIV-1 env protein All are within a predicted B cell epitope region (or within an experimentally described IEDB epitope) |
|---|
| Position within env protein | Epitope from IEDB | Type |
| 33 | KLWVTVVYGV | MHC binding |
| 36 | VTYYGYVPVWK | T cell/MHC binding |
| 108 | IISLWDQSL | MHC binding |
| 121 | KLTPLCVTL | T cell/MHC binding |
| 206 | PKISFEPIPIHYPAGFRA | MHC binding |

Viruses that modulate HIV-1 infection (for measles see above)

Dengue virus
(1, 2 or 3)

| VT Y+GV H and VT |
|---|
| Y GV V WK |
| 108: IIS DQ |
| 208: IEPIP |
| 242: VSTVQ |
| 252: RP V LL |
| 254: IVST LL |
| 256: STQLL |
| 264: SL EE+ |
| 264: SLAE |
| 265: LAE EV |
| 302: NTRKR |
| 302: NKRKR |
| 313: PGR TT |
| 335: RAK NT |
| 348: ESQ +QE |
| 363: QSSGG |
| 402: TEGSN |
| 523: LG STM |
| 570: VVGI AR |
| 580: VLAVE |
| 606: TA PWN |
| 685: F +VGG VG |
| 688: IM V GLV L |
| 691: VGGL |
| 722: PTPRG |

GB virus C

| 70: ATHAC D P+++ |

| 122: LTPL CV |

| 140: T SSSG EK |

| 209: SFE IIP |

| 213: IPI AG A |

| 252: RP+VS |

| 253: PIVS |

| 306: RKR + PG |

| 468: FR GGG D W |

| 521: ELG T A LT L G V |

| 523: LGAAG TM A M |

| 531: GA S+ T T QA |

| 574: K L ARVL |

| 581: LAVE LK |

| 582: AVE LK |

| 610: VPW AS |

| 686: IMI GL |

| 689: VG LVG and VG L GL |

| 729: R G GER DR |

| 738: GER IRLV |

| 807: LK VSSLNA |

| 828: RVIE |

| 830: IE QRA |

| 831: EVL RA |

| 831: EVL RA |

| 869: IM GL |

| 870: M VGG V L |

| 885: GGL P++ |

| 887: T DRI E V+G |

| 842: H RIR GL+ |

(Continued)
HTLV-2 infection appears to have a protective influence on HIV-1 infection. Should HTLV vaccines be developed, they may also have a role to play in relation to HIV-1.

As regards the shorter contiguous sequences and matches, the extensive homology of a single HIV-1 protein (env) with numerous phage and viral proteins (~72% of the currently sequenced virome) suggests that horizontal partial gene transfer from coinfecting DNA and RNA viruses to retrovirus, and/or vice versa, has proceeded on a massive scale during the evolutionary history of the AIDS virus and its ancestors. These include sequences from viruses infecting all kingdoms (e.g., bacteria, amoeba, fungi, plants, molluscs, insects, invertebrates, fish, birds, reptiles, and mammals) suggesting that these have at some time hosted the HIV-1 virus or its ancestors, along with other viruses, whose partial gene sequences have somehow been incorporated into the HIV-1 viral genome. There is no reason to suppose that this is not a feature of other retroviruses. As such sequences can subsequently be transferred to other genomes via retroviral insertion, this may partly explain the presence of phage and viral partial gene sequences within the genomes of plants, arthropods, fungi, nematodes, protozoa, mammals and man. The human proteome also contains multiple peptide consensi from bacterial, plant, and animal viruses.

Horizontal gene transfer from virus to retrovirus does not appear to have been specifically studied in the laboratory. However, gene exchange is common between viruses, and also between retroviruses, where, for example, recombination can lead to the development of novel HIV-1 viral strains. However, horizontal gene transfer has been reported from phages to bacteria, between bacteria, or from man to bacteria and indeed appears to be a common feature of all living matter. The acquisition of genomic DNA or RNA from infected higher species, by viruses, has also been proposed as a driving force in the evolution of viruses in general. Plant, arthropod, fungal, nematode, and protozoan as well as animal and human genomes also contain multiple retroviral and non-retroviral sequences. Clearly, this provides many potential routes for an interviral melange of genomic material. The direction or route of transfer cannot be imputed from a simple bioinformatics alignment, and the reasons for this homology require further laboratory testing. Again this evolutionary aspect is not the central theme of this analysis, and does not alter the implications ensuing from this homology.

All of the viruses for which vaccines are available, or which are known to favorably modulate HIV-1 viral load (Vaccinia, Dengue viruses, GB virus C, and measles) contain sequences matching those of the env protein. It is not possible to predict whether any particular sequence would potentially create cross-reactive anti-HIV-1 antibodies, but the Vaccinia virus as well as Dengue viruses, measles, and GB virus C contain several vatches within epitopes known to be able to label the AIDS virus in experimental studies (B cell, T cell, or MHC binding from IEDB: The amino acid sequences of these experimentally verified epitopes are appended at the bottom of the table). Note that these sequences often overlap within consecutive regions of the env protein. In the majority of cases shown, contiguous sequences were of pentapeptides, although longer gapped sequences are also illustrated.

| Viruses and Alignments with the HIV-1 env protein All are | (within a predicted B cell epitope region) |
|----------------------------------------------------------|------------------------------------------|
| 252 RPIVSTQLL                                           | MHC binding                              |
| 302 NYNKRKRIHHGPFYTTKNII                                 | B cell                                   |
| 311 IGPGRAFHT                                            | T cell                                   |
| 312 GPGRAFYTT                                            | MHC binding                              |
| 335 RAKWNTTLK                                            | MHC binding                              |
| 570 VGWIKQLQARVALERYLKD                                   | MHC binding                              |
| 606 TAVPWNASW                                            | MHC binding                              |
| 678 WLWYIKIFI                                            | MHC binding                              |
| 685 FIMIVGGGLV                                           | MHC binding                              |
| 686 IMIVGGLVGL                                           | MHC binding                              |
| 799 LLLQYWSQEL                                           | MHC binding                              |
| 828 RVIELQRA                                             | MHC binding                              |

Their start position (within the env protein of 856 amino acids) is marked as is their position with respect to predicted B-cell epitopes within the env protein (these are all within regions with an antigenicity index of greater than the server-set threshold of 0.35: see supplementary Table 1). Spaces within the sequences indicate nonidentical amino acids and + signs an amino acid with similar physicochemical properties. The gray shaded sequences are within sequences that have been described as epitopes in experimental studies (B cell, T cell, or MHC binding from IEDB: The amino acid sequences of these experimentally verified epitopes are appended at the bottom of the table). Note that these sequences often overlap within consecutive regions of the env protein. In the majority of cases shown, contiguous sequences were of pentapeptides, although longer gapped sequences are also illustrated.
Figure 1. Significant overall homologies of HIV-1 viral proteins with proteins from other viruses. Consensi and e values are shown in bold.

| Protein comparison | Alignment: between HIV-1 and other viral proteins |
|-------------------|--------------------------------------------------|
| HIV-1 env versus | | |
| AAA64569.1 | | |
| tsk-3 | | |
| IL-2 | | |
| virals | | |
| Envelope | | |
| Consensus | | |
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such short sequences. A further point to be considered is that this homology may enable different viruses to share the same binding partners in relation to the host proteome. Viruses also demonstrate this type of homology with human proteins, an ability that no doubt enables them to compete with their human counterparts as binding partners in the numerous host/pathogen interactomes that they use during their life cycles. HIV-1 and pox viruses both use the CCR5 chemokine receptor and such sharing may also influence the outcome of co-infection.

The differing matching peptide profiles for different HIV-1 viral strains also highlights the underlying complexity and shows that matching sequences will depend upon the HIV-1 strain, and presumably also the strain of the homologous virus. In relation to AIDS, this homology may have clinical application as infection or vaccination in relation to these viral homologues might be expected, in some cases, to confer cross-reactive immunity to HIV-1. There is indeed some evidence that this may be operative. For example, Vaccinia vaccination in HIV-1 infected subjects has been shown to inhibit HIV-1 viral replication in subsequent in vitro tests, but only in the CCR5 tropic HIV-1 Major M strain. These authors noted that the increase in the incidence of AIDS correlated with the successful eradication of smallpox and cessation of the use of Vaccinia vaccination. However, even within the M group of HIV-1 viruses, which displays tropism for the CCR5 chemokine receptor, considerable variation exists between the Vaccinia/HIV-1 peptide matches.

In a small study (four patients), hyperimmunization with the killed poliomyelitis (Salk) vaccine was also shown to increase the T cell count and to improve symptoms in HIV-1 infected patients. Influenza vaccination with the killed poliomyelitis (Salk) vaccine was also shown to increase the T cell count and to improve symptoms in HIV-1 infected patients. Influenza vaccination has also been reported to increase HIV-1 replication in some patients, perhaps due to the ability of the influenza virus to inhibit viral defense pathways. Both measles or GB virus C infection are also known to decrease the HIV-1 replication in non-HIV-1 patients also results in the suppression of HIV-1 replication in vitro. However, this was not observed in HIV-1 infected patients, and influenza vaccination has also been reported to increase HIV-1 replication in some patients, perhaps due to the ability of the influenza virus to inhibit viral defense pathways. Both measles or GB virus C infection are also known to decrease the HIV-1 viral load in infected patients, although other coinfections may perhaps worsen the effects of each other.

Vaccination can be a double-edged sword. For example, a lower titre of hepatitis B antibodies has been observed in several autoimmune disorders, including multiple sclerosis, suggesting a protective effect of infection. However, hepatitis B vaccination can have the opposite effect and provoke demyelinating lesions in certain cases.

### Table 2. Examples of Vaccinia virus homologues (from BLASTs of the relevant HIV-1 envelope proteins versus Ankara, GLV-1h68, Tian Tian, and L-IPV Vaccinia strains) compared with the envelope glycoprotein from a selection of HIV-1 viral strains (various subtypes from groups M, N, and O).

| Group M subtype A (isolate Z321) (Accession # P05881) | Group M subtype B (isolate BRU/LAI) (Accession # P03377) | Group M subtype B (isolate BH10) (Accession # P03375) | Group M subtype C (isolate ETH2220) (Accession # Q75008) |
|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| 340: DTLSKV                                           | 187: CSFNIS S                                         | 524: GAAGST                                          | 154: CSFNNI                                          |
| 388: TSGLF                                            | 529: GAAGST                                           | 352: KNKNT                                           | 391: LELFN                                           |
| 492: GAAGST                                           | 303: KLDI ID                                          | 383: TSGLF                                           | 429: GILMC                                           |
| 488: VVKIEXP                                          | 493: VVKIEXP                                          | 392: SNINN                                           | 512: GAAGST                                          |
| 617: KSQSD                                             | 705: A LSIVN                                          | 574: HLRDQ                                           | 629: IIVYN                                          |
| 644: NLIEE                                            |                                                         |                                                      | 690: LSIVN                                           |
| 702: LL LSIN                                           |                                                         |                                                      | 685: IIFAV                                           |
| 703: SIIN                                             |                                                         |                                                      |                                                     |
| 841: LNIP                                             |                                                         |                                                      |                                                     |

| Group M subtype D (isolate Z84) (Accession # P05882)  | Group M subtype F1 (isolate VI850) (Accession # Q9QS07) | Group M subtype G (isolate 92NG083) (Accession # O41803) | Group M subtype H (isolate 90CF056) (Accession # O70902) |
|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| 63: EAHNI                                              | 377: TSGLF                                            | 329: NVSR                                             | 661: WFDIS                                           |
| 197: NTNYT Y                                          | 386: SNNGT                                            | 352: KNKNT                                            | 690: LSIVN                                           |
| 291: NVNKTII                                          | 678: LSIVN                                            | 383: TSGLF                                            | 752: LSIFS                                           |
| 364: LNQTT                                            | 696: LIPSP                                            | 392: SNINN                                            |                                                     |
| 495: VV IEP                                           | 753: IAARI                                             | 473: KTVK+k                                           |                                                     |
| 531: GAAGST                                           | 678: ALKYL                                            | 510: GAAGST                                           |                                                     |
| 771: YLGNL                                            | 817: LNIP                                             | 688: LSIVN                                            |                                                     |

| Group M subtype J (isolate SE9173) (Accession # Q9WC69) | Group M subtype K (isolate 96CM-MP535) (Accession # Q9QBY2) | Group N (isolate YBF106) (Accession # Q9IDV2) | Group O (isolate ANT70) (Accession # Q77377) |
|---------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| 146: SPEIM N                                           | 378: VEHLEP                                               | 74: LLLTV                                          | 254: QLILN                                        |
| 180: INSND                                             | 448: NTHNE                                               | 79: TEYFN                                          | 544: HTLLK                                        |
| 194: TSVIK                                             | 510: GAAGST                                              | 134: +RTEKD                                         | 696: RVIIM                                         |
| 482: VVLELP                                            | 732: VRLVS                                               | 156: DRKK                                           | 698: IMVL                                          |
| 615: DIWEN                                             | 797: AISLL                                               | 250: QLILN                                         | 704: IVKNI+G                                       |
| 691: IIFAV                                             |                                                           | 476: VSREK                                         | 787: LKDSAI                                       |

Identical peptides (HIV-1 = Vaccinia) were analyzed for B cell antigenicity using the BepiPred server and those predicted as epitopes are highlighted in bold.
been shown that the HIV-1 proteome displays a similar type of homology with the human proteome and the problems of autoimmunity in relation to certain of these vaccines need to be addressed.\(^{31}\) Nevertheless, Vaccinia virus vaccination does reduce the HIV-1 viral load for the common CCR5 tropic strain, \textit{in vitro}, and a resumption of smallpox vaccination might be expected to be of benefit in certain cases, as already suggested.\(^{4}\) It would be premature to suggest the immediate use of other available vaccines as preventive agents without further research into the question. A more in-depth analysis of the viral homology of the env glycoprotein and of other HIV-1 proteins and strains is also necessary, and, given the scale of the phenomenon, which also applies to millions of viral/human and bacterial/human short consensi.\(^{17,37}\) It is clear that the development of powerful algorithms is necessary for this purpose. However, the results with the Vaccinia virus are promising and suggest that this homology may be harnessed to good effect. Whether other available vaccines could confer cross-reactive immunity remains to be assessed. These are often used in HIV-1 positive patients, once HIV-1 is present,\(^{30}\) but their use as potential preventive agents, given prior to HIV-1 infection, merits further study.

A further point to consider is the microbiome in AIDS patients. If so many viruses, and probably also bacteria and other pathogens, resemble HIV-1 viral proteins, it is possible that certain species could exert beneficial (or deleterious) effects. Sequencing of the various microbiota in AIDS resistant and nonresistant patients may, thus, be of value as such analyses may well be able to identify protective viral or bacterial strains. Microbiomes can exert a powerful influence on disease. For example, the intestinal microbiome is able to influence obesity, cardiovascular disease, and inflammatory bowel disease,\(^{39}\) and its manipulation in relation to HIV-1 is already attracting attention.\(^{40}\) Indeed, probiotic yoghurt containing \textit{Lactobacillus rhamnosus Fiti} is able to increase the CD4+ cell count in HIV-1 infected patients.\(^{41}\)

HIV-1 vaccine development using attenuated Ankara Vaccinia strains, containing HIV-1 proteins, is already under development.\(^{42}\) The most immediately relevant conclusion of this study is that the beneficial effects of unmodified Vaccinia vaccination in HIV-1 infected patients, \textit{in vitro}, may well be related to cross-reactive immunity due to Vaccinia/HIV-1 homology, and that, as previously suggested\(^{41}\) a resumption of Vaccinia/ smallpox vaccination might have a significant effect on the AIDS pandemic, even if only effective against certain strains.

Clearly further work is needed, both \textit{in vitro} and \textit{in vivo} to analyze these effects. Rather than suggest specific proposals for vaccine development or the use of already available vaccines, the main purpose of this article is to draw attention to this extensive protein homology, which may have far-reaching implications in this and other diseases. A similar bioinformatics approach may be relevant to other recalcitrant viruses, bacteria, and pathogens and the current treasury of available vaccines may well find uses in diseases other than those for which they were designed. Other HIV-1 proteins and numerous strains of both the HIV-1 and other viruses also require analysis perhaps enabling the construction of more effective epitopes. The wheel has turned full circle since Edward Jenner’s observation over 200 years ago that cowpox prevented smallpox, as, if this is effective, the same phenomenon and the same viruses may have a role to play in relation to today’s viral scourge.

## Declaration of interest

The author declares no conflict of interest.

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