Volume 242, number 1, 9–21 FEB 06590 December 1988

Predictions of linear T-cell and B-cell epitopes in proteins encoded by HIV-1, HIV-2 and SIV_{MAC} and the conservation of these sites between strains

Markéta J.J.M. Zvelebil[+], Michael J.E. Sternberg[+*], John Cookson[°] and Anthony R.M. Coates[†]

[+]*Laboratory of Molecular Biology, Department of Crystallography, Birkbeck College, Malet Street, London WC1E 7HX,* [°]*Hill Computer Centre* and [†]*Department of Medical Microbiology, The London Hospital Medical College, Turner Street, London E1 2AD, England*

Received 13 October 1988

An important consideration in the design of vaccines to prevent HIV-1 infection effective against different strains is the amino acid sequence conservation of antigenic determinants. Even one amino acid change can destroy the antigenicity of a site for the antibody or T-cell receptor. The comparisons of predicted T- and B-cell epitopes between human HIV-1, HIV-2 and monkey SIV_{MAC} AIDS viruses are presented. The three major gene products (env,gag and pol) were examined. A number of epitopes were identical between strains of HIV-1. Our analysis highlights the problem of designing an effective HIV-1 and HIV-2 vaccine and also the problem of testing human vaccines in monkey models.

AIDS; HIV-1; HIV-2; SIV_{MAC}; Vaccine design; Antigenic epitope

1. INTRODUCTION

There is no effective vaccine for the prevention of AIDS (Acquired Immune Deficiency Syndrome). In designing a vaccine for this disease, consideration should be given to epitope sequence variation between strains of the human immunodeficiency virus type-1 [1–4] because a successful vaccine should be effective against a range of isolates. Furthermore, if epitopes were identified which are shared between human immunodeficiency virus type-1 (HIV-1) and type-2 (HIV-2) [5] a common HIV vaccine for these two strains could be feasible. SIV_{MAC} causes an AIDS-like disease in rhesus macaque monkeys [6]; therefore, if a section of the chain is conserved between HIV-1, and SIV_{MAC} it could lead to testing of the effect of HIV-1 peptides in monkeys. In this paper we use the nucleotide-derived protein sequences of HIV-1 strains, HIV-2 and SIV_{MAC} to predict areas of sequence homology which contain antigenic B-cell and T-cell determinants. We consider the three major gene products: gag, pol and env.

Research has concentrated on the development of an envelope vaccine [7–11] because certain retroviral envelope proteins [12] do confer antibody-mediated protection against viral challenge in animals. So far HIV-1 envelope vaccines [13] have failed to protect chimpanzees against infection. We have suggested [14,15] that the search for a vaccine should not only include env, but also gag and possibly pol gene products. This proposal is based upon the observation [16] that T-cell epitopes of the core protein of hepatitis-B virus induce T-cell help of B lymphocytes. This results in the production of antibody against the surface antigen. Furthermore, preliminary ex-

Correspondence (present) address: M.J.J.M. Zvelebil, Biomolecular Computing Laboratory, Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London WC2A 3PX, England

* *Present address:* Biomolecular Computing Laboratory, Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London WC2A 3PX, England

Published by Elsevier Science Publishers B.V. (Biomedical Division)
00145793/88/$3.50

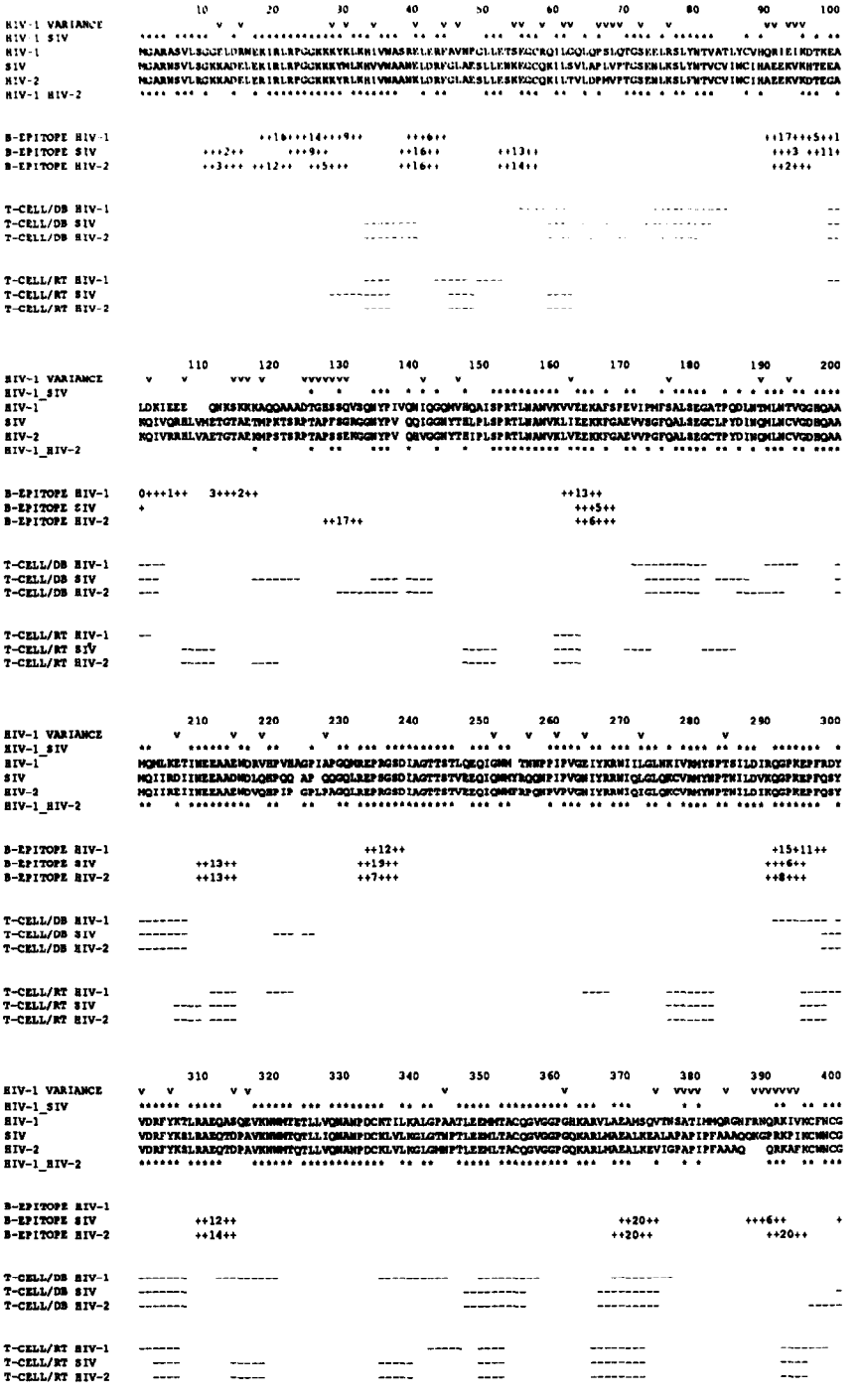


Fig.1. The alignment of gag HIV-1, HIV-2 and SIV_{MAC} sequences. The '*' on the top row indicates identities between HIV-1 and SIV_{MAC}. '*' on the bottom row indicates identities between HIV-1 and HIV-2. A '+' denotes the core prediction for the B epitopes where the number gives the rank peak height. A '–' illustrates predicted positions for T epitopes by both the DeLisi and Berzofsky (BD) method and the Rothbard and Taylor (RT) method. A 'v' denotes an inter-strain variable position and a 'g' indicates where it was necessary to insert a gap into the alignment.

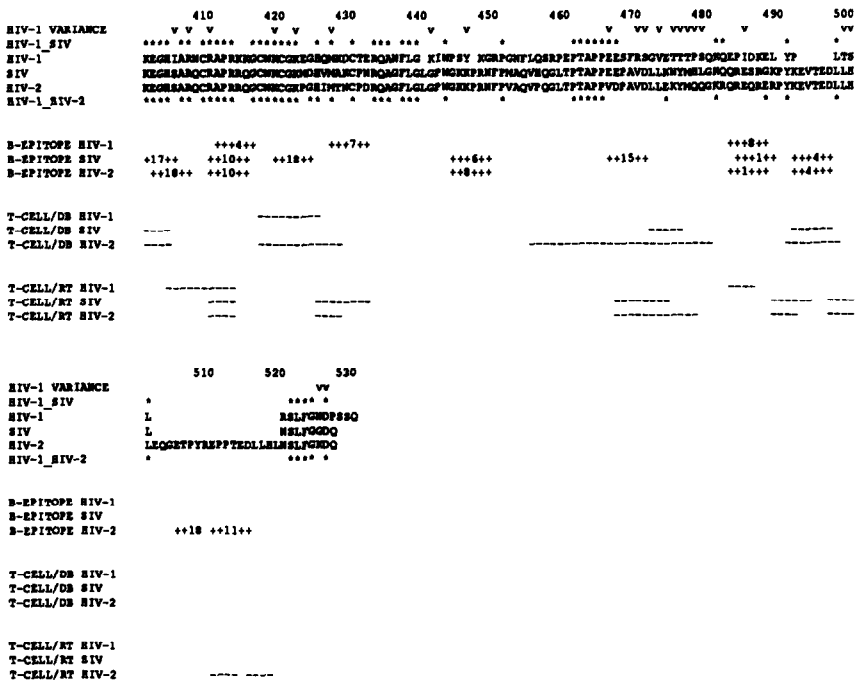


Fig.1 (contd).

periments [17,18] suggest the core antigen of hepatitis-B may induce protection in chimpanzees against viral challenge. Whether any of this applies to an AIDS vaccine is unknown, but T-cell-mediated immunity against HIV-1 env and gag proteins, both helper and cytotoxic, has been recorded [19–21]. In addition antibody against HIV-1 core (gag) antigen disappears, in many patients, prior to the onset of the disease, but it is not clear whether this indicates that an anti-gag immune response prevents the onset of the disease [22] or whether it merely accompanies progression towards AIDS.

In this paper, we have performed epitope predictions for T- and B-cell sites. T-cells may recognize different [23] parts of the chain from B cells but there is evidence that protective B epitopes of influenza virus overlap with T epitopes [24].

2. MATERIALS AND METHODS

The studies were carried out on the HIV-1_{LAV} virus, the simian virus (SIV_{MAC}) and HIV-2_{ROD}. The sequences for the HIV-1 virus were obtained from the Protein Information Resource Databank (see [15] for further details). The sequences for other HIV-1 strains, SIV_{MAC}, HIV-2 were obtained from the Los Alamos National Database [25].

2.1. *Sequence variation between the HIV-1 strains*

Ten gag, 13 env and 8 pol HIV-1 sequences were aligned by the method of Barton and Sternberg [26] to investigate inter-strain variation. In figs 1–3 a 'v' denotes inter-strain variation for HIV-1 and a 'g' denotes the introduction of a gap into the alignment. In tables 1 and 2, %SI denotes the identity between HIV-1 isolates within a predicted epitope.

2.2. *Sequence variation between HIV-1, SIV_{MAC} and HIV-2*

A multiple alignment of HIV-1, SIV_{MAC}, and HIV-2 sequences was obtained [26]. In figs 1–3 an identity between HIV-1 and SIV_{MAC} is indicated by a * on the top row, while identities between HIV-1 and HIV-2 are indicated by a * on the bottom row of the alignment.

2.3. *Principle of analyses*

Predictions of B-cell and T-cell epitopes (see sections 2.4 and 2.5) were performed on the HIV-1, HIV-2 and SIV_{MAC} sequences (figs 1–3). These figures provide information to guide vaccine design based on many different criteria. For example, peptides might be selected on sequence conservation or on regions of high variation. In this paper we analyse conservation of sequences and of predicted antigenic epitopes. Predicted epitopes were taken to be at least 12 residues long as peptides of this length have frequently been shown to contain an epitope [27–29]. This analysis, of course, considers only linear epitopes.

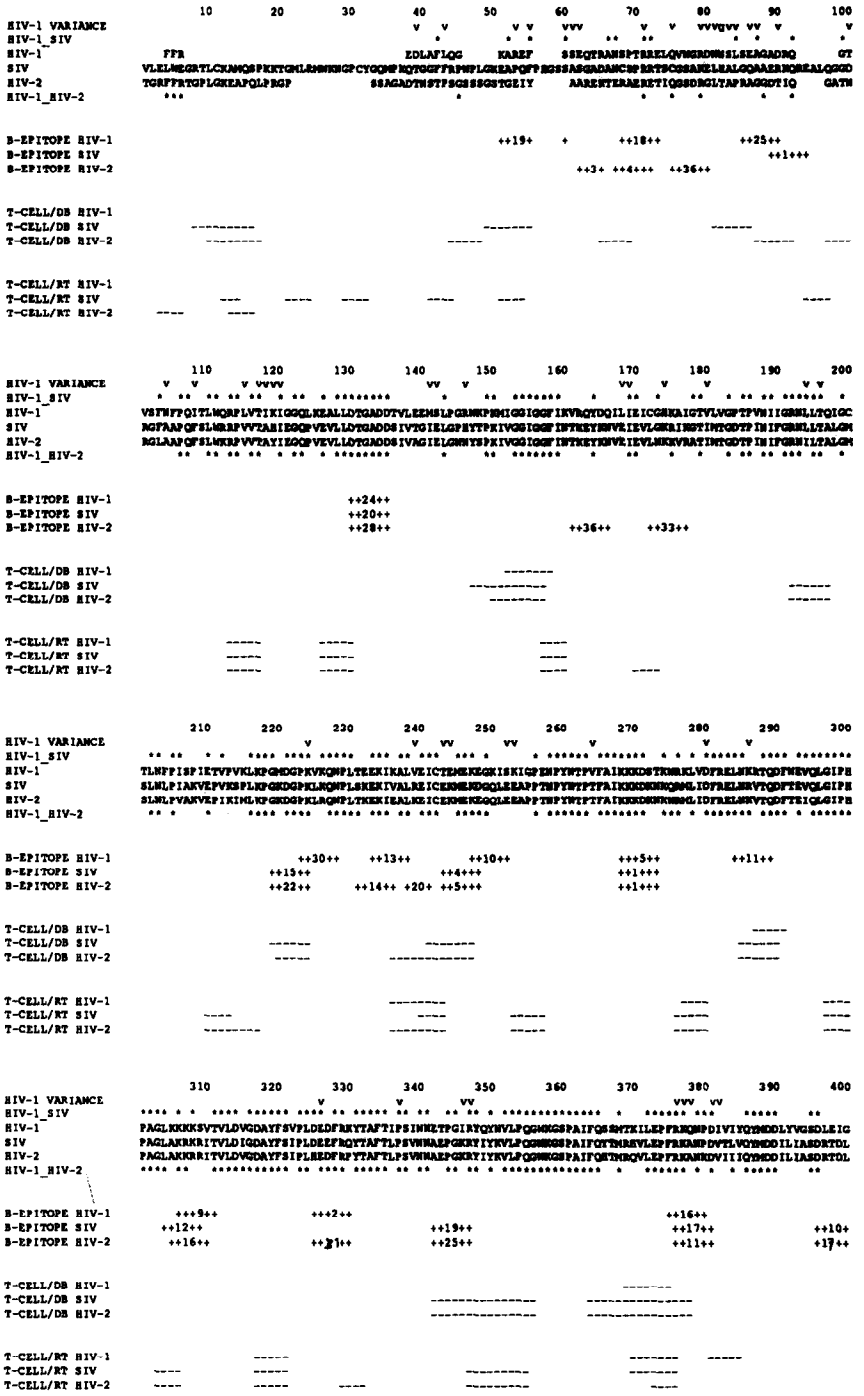
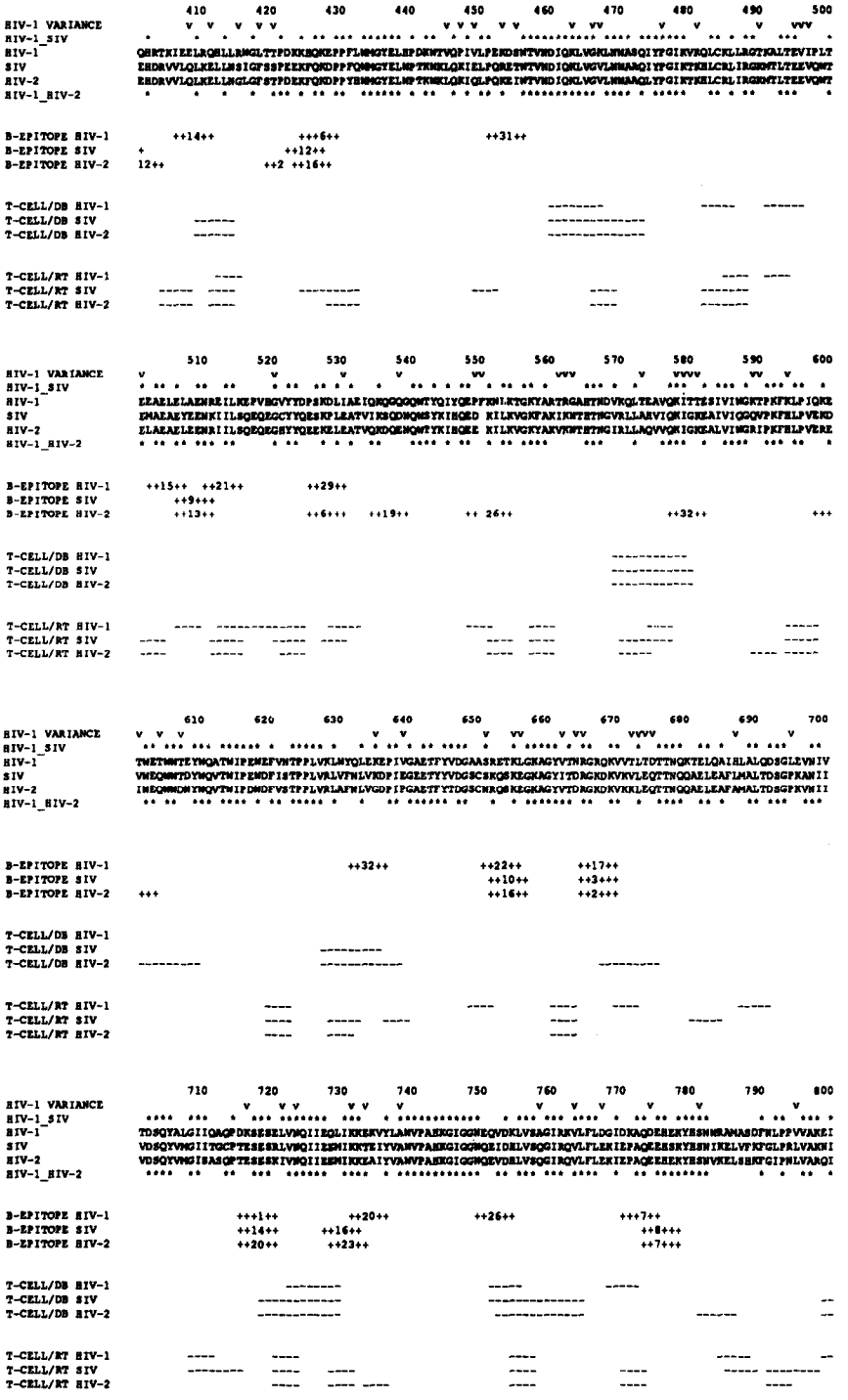

HIV-1 VARIANCE
HIV-1_SIV
HIV-1
SIV
HIV-2
HIV-1_HIV-2
B-EPITOPE HIV-1
B-EPITOPE SIV
B-EPITOPE HIV-2
T-CELL/DB HIV-1
T-CELL/DB SIV
T-CELL/DB HIV-2
T-CELL/RT HIV-1
T-CELL/RT SIV
T-CELL/RT HIV-2

Fig.2 (contd).



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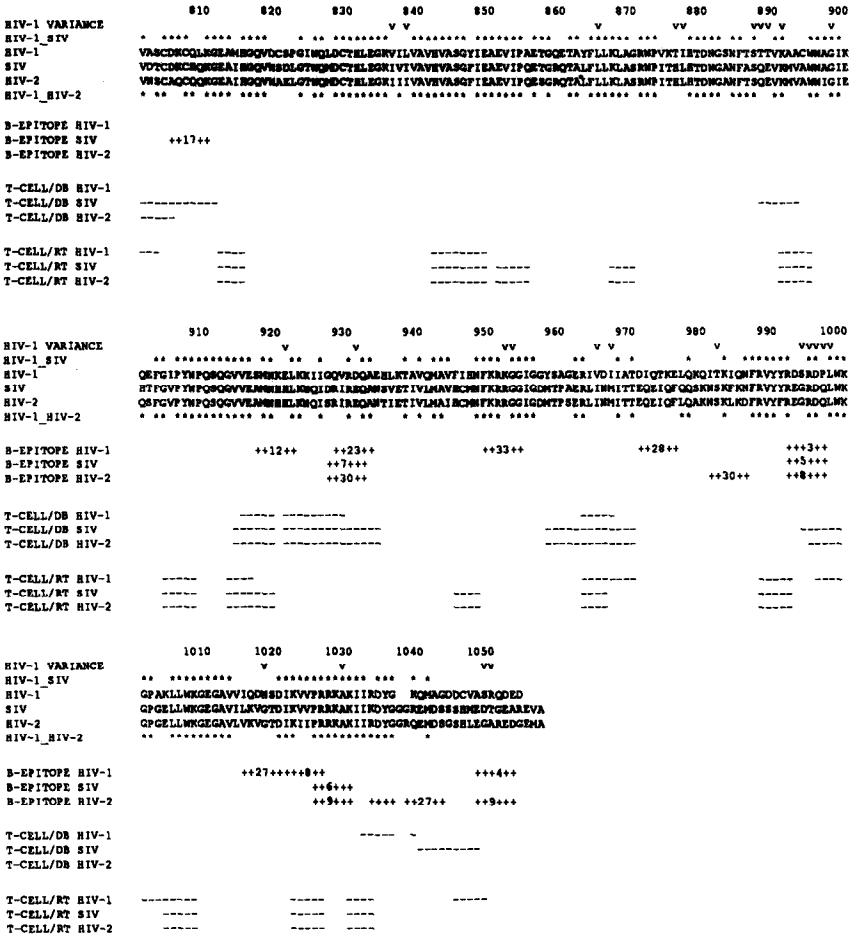

Fig.2. The alignment of pol HIV-1, HIV-2 and SIV_{MAC}.

The identity between HIV-1 and HIV-2 was calculated for positions in the HIV-1 predicted epitope irrespective of whether an epitope was predicted in HIV-2 (denoted as HIV-1 %1-2). Similarly HIV-1 %1-S denotes the identity between HIV-1 and SIV_{MAC}. Other measures of sequence identity between epitopes were considered but these did not markedly alter the results. Tables 1 and 2 list all B and T epitopes with %SI of 100%. Epitopes with 1 or 2 sequence variable positions are reported in the text.

2.4. *B epitopes*

B-cell epitopes were predicted by the algorithm of Hopp and Woods [30] which searches for a local maximum in a hydrophilicity profile smoothed over 6 residues. Hydrophilic peaks were selected in order of decreasing hydrophilicity. The 6 residue predicted B-epitope core (denoted by a '+' in the figures) was extended on either side by 3 residues to obtain a 12 residue long polypeptide (called the predicted epitope). In our previous study [14,15] we concentrated on B epitopes that did not occur within a predicted secondary structure. Because of the sequence variation between HIV-1, HIV-2 and SIV_{MAC}, different predictions of secondary structure were obtained (results not shown). Given the limited accuracy of secondary structure predictions, a structural restriction on B epitopes would unduly complicate the analysis.

2.5. *T epitopes*

Two algorithms to predict T-cell epitopes were applied, and the results denoted by a '−' in the figures. (a) The method of DeLisi and Berzofsky [23] calculates the amphipathicity of a section 11 residues long and regions with an α-helix periodicity are identified as possible T-cell epitopes. (b) The procedure of Rothbard and Taylor [29] scans for a linear pattern composed of a charged residue or a glycine, followed by 2 or 3 hydrophobic amino acids and terminated by a charged or polar residue.

The predicted T epitope regions can be longer or shorter than the 12 residues defined for the B epitopes. In this paper, the core prediction was extended towards the N- and C-termini to a polypeptide of minimum 12 residues or to as long as T epitopes positions were predicted by either method and overlapped by at least one position.

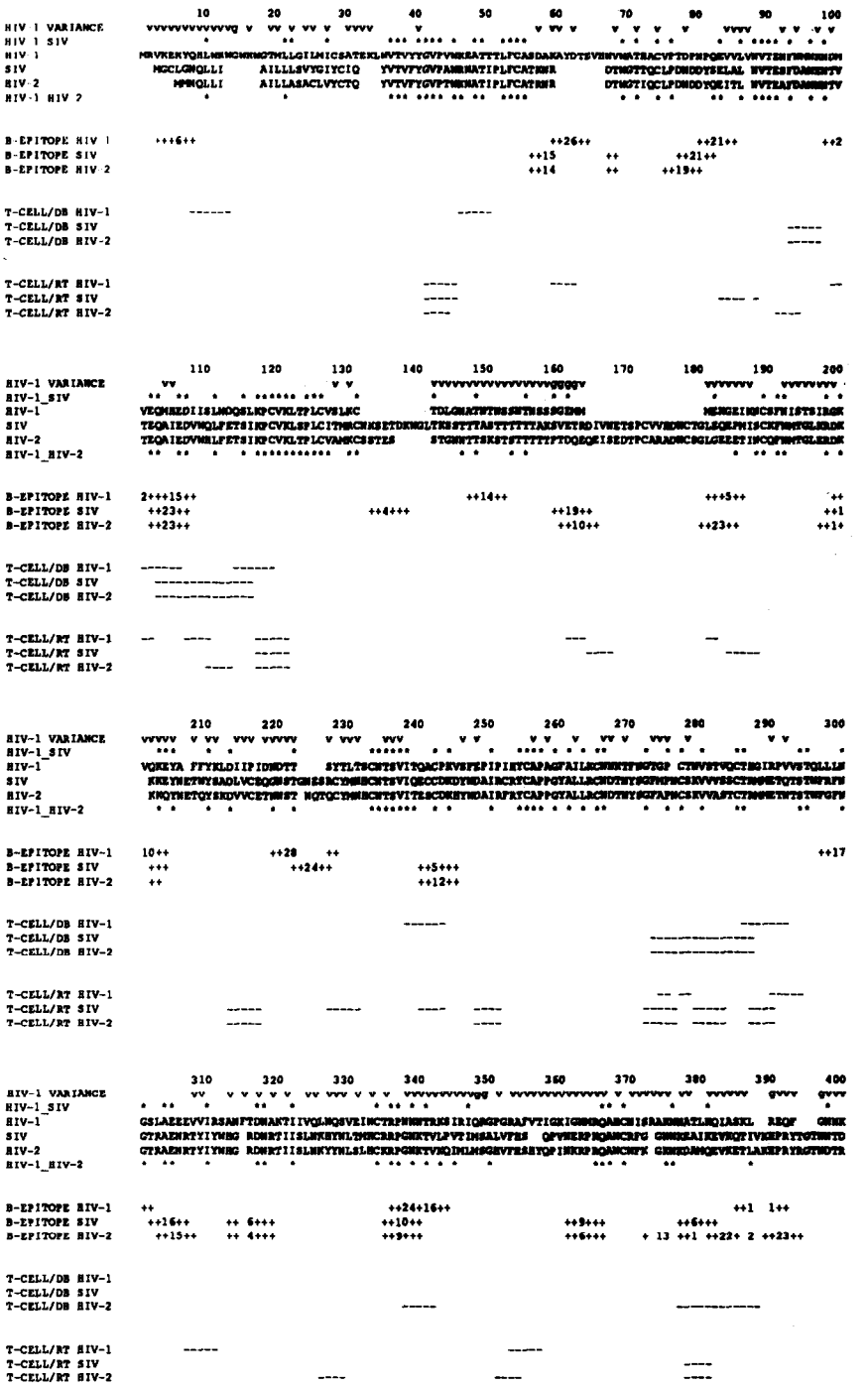

Fig.3 (contd).

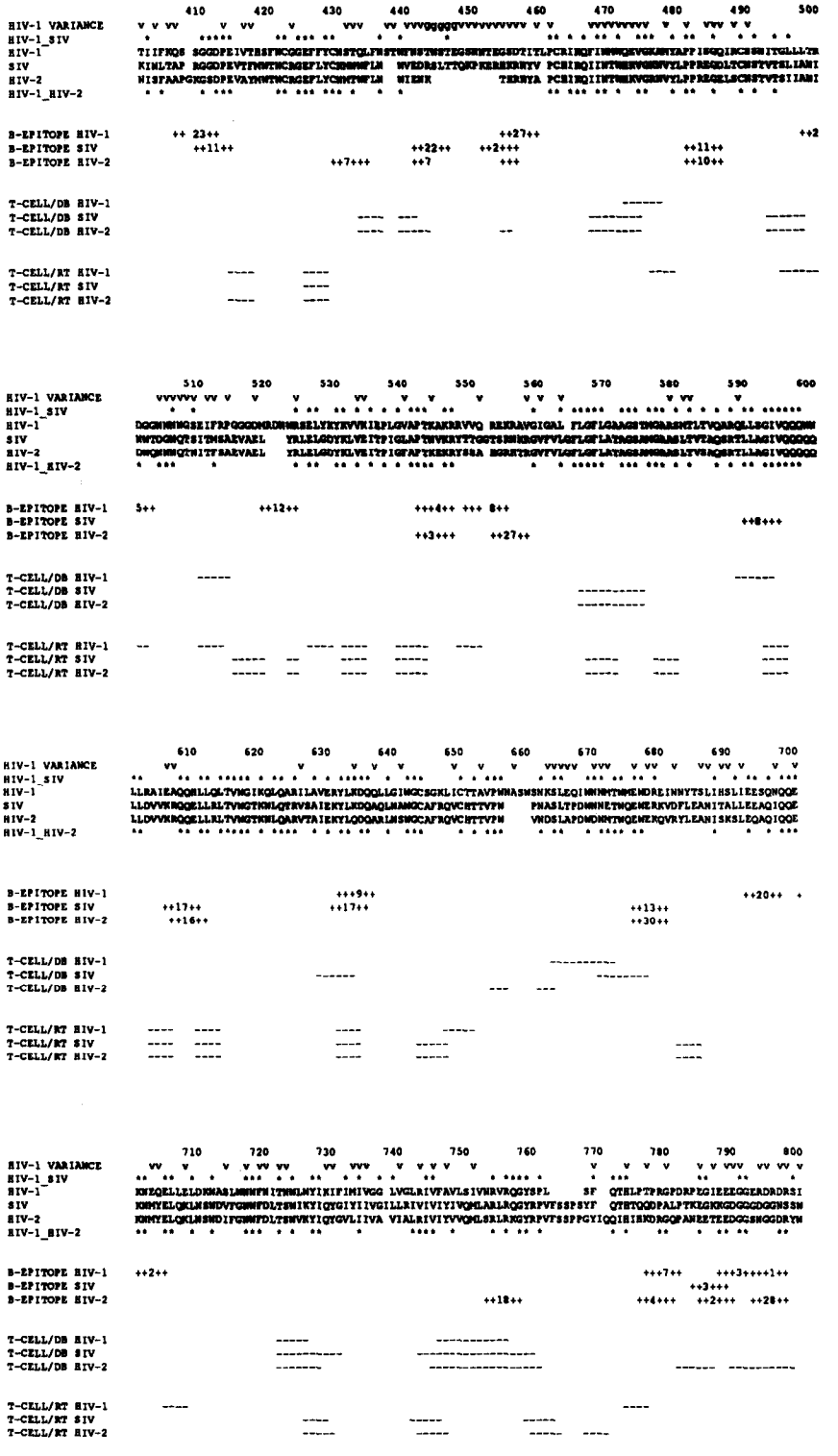

Fig.3 (contd).

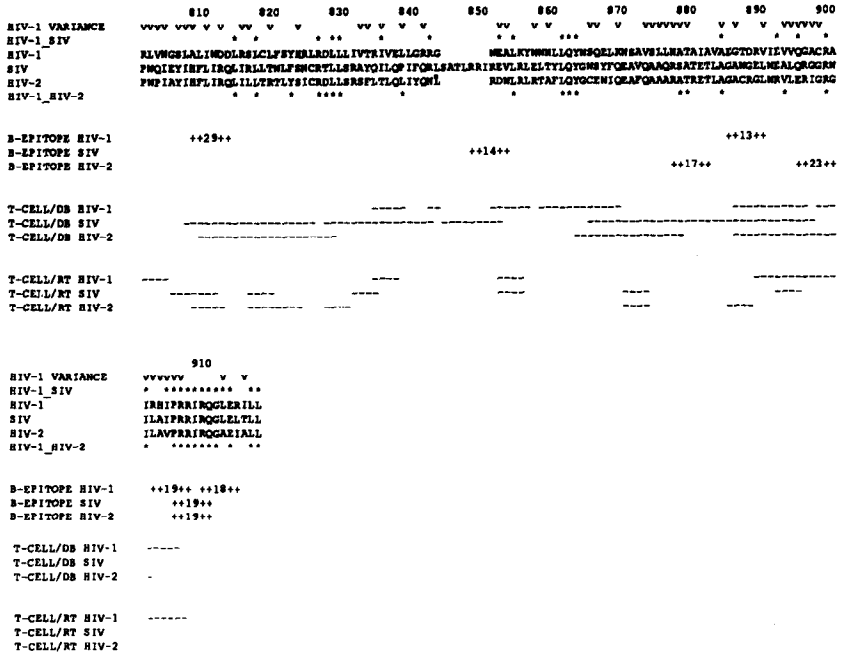

Fig.3. The alignment of env HIV-1, HIV-2 and SIV_{MAC}.

Table 1

The predicted B epitopes with %SI = 100 in HIV-1

HIV-1		HIV-2		SIV_{MAC}	
Epitope numbers	Epitope sequence	Epitope numbers	HIV-1 %1–2	Epitope numbers	HIV-1 %1–S
Pol					
128–139	ALLDTGADDTVL	128–139	67	128–139	67
265–276	FAIKKKDSTKWR	265–276	83	265–276	75
303–314	GLKKKKSVTVLD	301–313	67	301–312	67
421–432	PDKKHQKEPPFL	416–427	58	419–430	58
		420–431	58		
507–518	LAENREILKEPV	503–514	50	503–514	33
746–757	ISGNEQVDKLVS		75		67
968–979	IATDIQTKELQK		33		25
Gag					
230–241	QMREPRGSDIAG	229–240	92	229–240	83
288–299	LDIRQGPKEPFR	288–299	83	288–299	75
Env					
294–305	STQLLINGSLAE		50	299–310	50

The epitope numbers denote the positions of the predicted epitopes in the figures. The HIV-1 epitope sequence is given. If an epitope is found in corresponding regions in HIV-2 or SIV_{MAC} then their position numbers are given. %HIV-1 is defined in procedures

Table 2

The predicted T epitopes with %SI = 100% in HIV-1

HIV-1		HIV-2		SIV_{MAC}	
Epitope numbers	Epitope sequence	Epitope numbers	HIV-1 %1-2	Epitope numbers	HIV-1 %1-S
Pol					
123–134	QLKEALLDTGAD	123–134	75	123–143	75
150–161	KMIGGIGGFIKV	150–161	67	147–160	67
293–304	EVQLGIPHPAGL	293–304	92	293–304	100
314–325	DVGDAYFSVPLD	314–325	83	314–325	83
502–513	EAELELAENREI		67		58
615–626	IPEWEFVNTPPL	615–626	75	615–626	75
704–715	QYALGIIQAQPD		50	706–717	50
796–807	VAKEIVASCDKC	797–808	58	799–810	75
808–819	QLKGEAMHGQVD	808–819	67	808–819	67
840–851	AVHVASGYIEAE	840–851	92	840–851	92
901–912	QEFGIPYNPQSQ	901–912	83	901–912	75
Gag					
347–359	LEEMMTACQGVG	346–357	92	346–357	92
Env					
42– 53	VPVWKEATTTLF		67		58
111–124	LWDQSLKPCVKLTP	103–116	71	103–116	64

3. RESULTS

The HIV-2 and SIV_{MAC} sequences are far more homologous to one another than either are to HIV-1. We pay particular attention to regions where B and T epitopes overlap because it has been shown that protective epitopes in influenza virus contain overlapping B and T epitopes [31]. All residue numbers refer to the alignment numbers used in the figures.

3.1. *Analysis of the gag gene*

Fig.1 illustrates the alignment and prediction of the gag gene product. 50% of residues are conserved between HIV-1, SIV_{MAC}, and HIV-2. Ten B epitopes were located that had 2 or less HIV-1 inter-strain variable positions. Two B epitopes were found in which there was total sequence identity between the thirteen HIV-1 isolates (100% SI). Both regions have corresponding HIV-2 and SIV_{MAC} predicted B epitopes with reasonable sequence conservation to HIV-1. Part of the 288–299 B epitope region (LDIRQGPKEPFR) has also previously been identified as a promising candidate for vaccine studies [14,15]. There are four B epitopes with one inter-strain variable position (15–26, 158–169, 290–301, 480–492). All but 480–492 have overlapping HIV-2 and SIV_{MAC} predicted B epitopes. Four B epitopes had two inter-strain variable positions (20–31, 95–106, 99–113, 308–419). Only 20–31 and 308–319 had a HIV-2 B epitope associated with them while 20–31, 95–106 and 308–319 a SIV_{MAC} B epitope. Only the region 20–31 has a HIV-2 and SIV_{MAC} sequence with high sequence identity to HIV-1. Thus, although gag contains 2 B epitopes that have no inter-strain variability, they are not identical to either HIV-2 or SIV_{MAC}. Therefore if one residue difference disrupts the antigenicity of the epitopes, it is not possible to produce a HIV-1 B epitope that will be effective against HIV-2 infection or that could be tested in SIV_{MAC}. However, if peptides shorter than 12 residues are considered then there is an epitope (15–26 in HIV-1) that has 8 residues for which there is 100% sequence identity with SIV_{MAC}.

Only one T epitope (347–358) has no inter-strain variation. In HIV-2 and SIV_{MAC} there are corresponding T epitopes in this region and the sequence homology to HIV-1 is high. Eight T epitopes are found that have one inter-strain variable position (73–84, 156–167, 170–181,

198–209, 215–226, 273–284, 335–346, 365–376) and further 8 T epitopes are located that have 2 inter-strain variable positions (96–107, 187–198, 207–218, 260–271, 291–307, 311–322, 415–426, 479–491). Of the 17 T epitopes with less than three sequence variations between HIV-1 strains, 13 are in the p24 protein.

The B epitope in position 288–299 has a T epitope region overlapping at positions 291 to 307 which has two inter-strain variable positions. The only T epitope with no inter-strain variation (347–358) has no overlapping predicted B epitope.

3.3. *Analysis of the pol gene*

The pol sequence is as well conserved as the gag, 49% identity between the three aligned sequences and there are a considerable number of B and T epitopes found with no inter-strain variation. Seven B epitopes are found with 100% SI. But none have HIV-1 %1-2 and HIV-1 %1-S of 100%. However, one HIV-1 B epitope (1018–1029) has 8 residues that are fully conserved to the predicted B epitope in SIV_{MAC}. Ten B epitopes were located with one inter-strain variable position (220–231, 230–241, 281–292, 322–333, 499–510, 522–533, 914–925, 925–936, 1012–1023, 1018–1029). Six of these had overlapping B epitopes in HIV-2 and only 4 in SIV_{MAC}.

A total of 11 T epitopes are identified in the pol product that has no inter-strain variation. One of these, epitope 293–304 has 100% sequence identity to SIV_{MAC}, which also has a T epitope predicted. Between HIV-1 and HIV-2 there is only one residue difference and also a T epitope is predicted in the same position. This T epitope prediction overlaps with a B epitope prediction (303–314) that also has no inter-strain variable position. Further 10 T epitopes are found that have only one inter-strain variable position (273–284, 284–295, 478–489, 512–524, 683–694, 749–760, 780–791, 910–921, 1019–1030, 1026–1039).

3.4. *Analysis of the env gene*

There is a low homology (28% identity) between the three env sequences. One B epitope is found that has no inter-strain variation. However, this B epitope has no corresponding prediction in HIV-2 and although there is an overlapping B epitope prediction in SIV_{MAC} the sequence homology is very low. No B epitopes with only one inter-strain variable position were found. There are five B epitopes with two inter-strain variable positions (100–111, 516–527, 539–550, 546–558, 628–639).

Only two T epitopes that are conserved between the HIV-1 isolates are found in the env product. One (42–53) has no corresponding T epitope prediction in either HIV-2 or SIV_{MAC}. The other (111–124) has overlapping T epitope predictions in HIV-2 and SIV_{MAC} but the sequence homology between these and HIV-1 is low. Three T epitopes with one inter-strain variable position (37–48, 521–532, 586–600) and nine T epitopes with two inter-strain variable positions (283–297, 527–538, 535–546, 544–556, 599–610, 606–617, 627–638, 643–654, 764–757) were located. None showed high sequence homology to HIV-2 or SIV_{MAC}.

4. DISCUSSION AND CONCLUSIONS

Antigen prediction techniques were used to analyse the potential effect of HIV epitope sequence variability on AIDS vaccine design. This study, being based on predictions, is intended as a guide for experimental vaccine design. For the B-epitopes, the predictions with the higher rank order of hydrophilicity (figs 1–3) will be more accurate [30]. The highest peak is nearly always antigenic [30]. For example, the env B epitope 787–800 is antigenic [32] and contains two predicted epitopes of rank 1 and 3. The accuracy of T epitope predictions has been less well studied. However, two predicted T epitopes [15] have subsequently been shown [33] to be part of experimentally verified T-cell sites (peptides 105–117, 465–480). Env, gag and pol each code for several protein products that result from proteolytic cleavage of the initial polyprotein gene product. If a predicted epitope includes a cleavage site then this epitope might not be antigenic. However, in cells infected with a related retrovirus (equine infectious anemia virus), uncleaved and partially cleaved polyproteins have been shown to be antigenic [34]. Thus peptides that span protease cleavage sites might be antigenic. Accordingly we have included them in this study but the location of these cleavage sites should be considered in the interpretation of experimental results.

We addressed three specific problems. Firstly, we investigated the likelihood of finding a single HIV-1 vaccine which might protect an individual

against a range of HIV-1 isolates. In other microorganisms neutralising antibody against surface antigens, such as envelope, confers protection and accordingly the most promising candidates for de novo protection against HIV infection are the env proteins. In env there was only one predicted B epitope (294–305) which was found to be conserved between the 13 isolates considered. The hydrophilicity is ranked 17th, which indicates a low accuracy of prediction. In contrast, the B epitope 787–800, which has the highest rank, is poorly conserved between HIV-1 strains and only 5 out of its 14 residues were found in all the isolates which were studied. This suggests that env from one HIV-1 strain is unlikely to induce protective antibody-mediated immunity against a range of wild HIV-1 strains unless the 294–305 epitope is effective as a vaccine. In gag two B epitopes are conserved between all strains but in pol seven B epitopes are conserved. In viruses, a major component of the T-cell response is directed at internal proteins. In HIV-1 two T epitopes are fully conserved in all strains for env, one for gag and 11 for pol. If a polypeptide from a single strain is to be effective against all HIV-1 isolates in an outbred population such as man, then this analysis indicated T epitopes from pol as the most promising candidate. The analysis highlights the need in animal studies to challenge with the same strain of virus which was used to immunize. A problem with this approach might occur if epitope variation were to occur early after infection.

Secondly, we assessed the feasibility of using HIV-1 antigenic peptides in a monkey AIDS model, by searching for sections of the chain which are conserved between HIV-1_{LAV} and SIV_{MAC}. In env and gag, no predicted sites were 100% identical between HIV-1 and SIV_{MAC}. Pol had only one conserved site. Thus it is unlikely that HIV-1 peptides will confer protection against SIV_{MAC} challenge in the monkey if complete epitope sequence conservation is required.

Thirdly, the prospect for a single HIV-1 vaccine which would protect an individual against HIV-2 was addressed. In env, gag and pol no predicted B-cell and T-cell sites were 100% identical between HIV-1 and HIV-2, and so a single effective HIV-1/HIV-2 vaccine is unlikely to emerge.

Apart from T epitope based predictions in pol, a cocktail of peptides from different viral strains may be required as an effective vaccine against HIV-1. It is unlikely that this cocktail will be effective against HIV-2 and so additional peptides based on the HIV-2 virus will need to be introduced. The HIV-1 vaccines would be difficult to test in rhesus macaque monkeys because of considerable sequence variation between HIV-1 and SIV_{MAC}.

Acknowledgements: The MRC, AFRC and the Imperial Cancer Research Fund provided financial support. We thank Dr Geoff Barton and Dr D. Sia for advice.

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