Supporting Information

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SI Materials and Methods

Ten sets of HIV-1 Env peptides from four different clades were synthesized, two from clade A, two from clade B, 4 from clade C, and two from clade G. These 10 proteins were selected based on the following criteria: (*i*) they were from diverse isolates from within each clade (see Fig. 2); (*ii*) they were from different nations within each clade; (*iii*) they were embedded in a full length sequence, so a matched set of all HIV proteins could later be synthesized for subsequent studies; (*iv*) they were from recently sampled isolates at the time of the study design (all were sampled post-1999); and (*v*) they were not extreme outliers but instead typical of recently sampled isolates.

Each peptide set consisted of 212 peptides. All 212 overlapping peptides from each of the 10 sets of HIV-1 Env peptides were used to make the peptide matrices. These peptides include up to 10 variants for every 15-mer and give extensive global coverage of 9-mer fragments in the Los Alamos HIV database. Making all peptides for each of 10 proteins provides a straightforward and comprehensive way to track the total number of detected cross-reactive responses to natural proteins. To keep the peptides in synchronous alignment for all 10 proteins, given that the HIV envelope has many natural insertions and deletions, if an envelope protein had a natural deletion relative to the rest of the alignment, a peptide < 15 aa would be synthesized to span that peptide; if an envelope had a relative insertion, an additional peptide would be synthesized to span that peptide region; no peptides >15 aa were used. The PeptGen tool at the Los Alamos HIV database was used for peptide design (http://www.hiv.lanl.gov/content/sequence/PEPTGEN/peptgen.html).

Table S1. The sequences of HIV-1 Env peptides

Subtype	Country	Year	Sequence	Accession
C	Uruguay	2001	TRA3011	AY563169
C	India	1999	01IN565–14	AY049711
C	Kenya	2000	KER2010	AF457054
C	South Africa	2001	J54Ma	AY463223
A	Cameroon	2001	1152NG	AY371163
A	Russia	2003	20_06_13	AY500393
B	Colombia	2001	PCM013	AY561237
B	Argentina	2000	ARMS008	AY037269
G	Cameroon	2001	4049HAN	AY371121
G	Spain	2000	X558	AF423760