

I-A

Best-Characterized HIV-1 CTL Epitopes: The 2013 Update

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Abstract

Over the last 15 years, the Los Alamos Immunology Database has posted regularly updated lists of best-characterized HIV-1 CTL epitopes (A-list). Here we provide an extensive overhaul of the A-list, applying expanded inclusion criteria that reflect new technologies and progress in the field. A few previously included, incorrect epitopes were removed or amended, and more than 35 newly identified epitopes were added. This updated A-list expands the number of well-described, fine-mapped and HLA class I restricted epitopes to more than 300, presented across more than 80 different HLA class I alleles. A number of considerations for optimal epitope mapping and for the assessment and interpretation of host immunity to HIV are discussed.

to relatively conserved epitopes [Brockman *et al.*, 2012; Ferrari *et al.*, 2011; Troyer *et al.*, 2009]. In addition, CTL responses associated with relative protection from HIV disease progression have an increased functional avidity and a superior ability to react with epitope variants [Berger *et al.*, 2011; Mothe *et al.*, 2012]. Interestingly, some of these studies employed CTL epitopes that can be restricted by HLA alleles associated with both slower and faster HIV disease progression, suggesting that the restricting HLA alleles can severely impact the *in vivo* “quality” of CTL responses [Frahm *et al.*, 2007; Leslie *et al.*, 2006]. Evidently, most of these studies rely heavily on the unequivocal identification of the targeted epitopes and their restricting HLA class I allele. The collection of such well-defined epitopes has been the central aim of our efforts to create and maintain a list of optimally defined epitopes at the Los Alamos HIV database, for which we here provide the 2013 update.

I-A-1 Introduction

Since the first description of HIV-specific T-cell responses 25 years ago by Walker *et al.* [1987], much has been learned about their *in vivo* induction, anti-viral activity, and role in HIV control. Combined studies of host genetic factors, viral sequence polymorphisms, viral fitness data and the fine mapping of virus-specific T-cell responses strongly suggest that the specificity of cytotoxic T-lymphocyte (CTL) responses and their HLA restriction are crucial determinants for viral control [Kiepiela *et al.*, 2007; Mothe *et al.*, 2011; Zuñiga *et al.*, 2006]. Data from *in vitro* viral replication inhibition assays show that CTL clones targeting Gag clearly outperformed other specificities, in particular, CTL targeting envelope proteins [Chen *et al.*, 2009, 2011], and may relate to the loss in replicative fitness when the virus has to escape from T-cell specificities

I-A-2 History and development of the CTL epitope A-list

Since 1995, we have maintained a list of the best-characterized HIV-derived CTL epitopes at the Los Alamos National Laboratory HIV Immunology Database, often referred to as the “Optimal CTL Epitope List” or “A-list” of HIV CTL epitopes. From an original set of 60 epitopes restricted by 20 (2-digit) HLA class I alleles in 1995, this list has grown to over 270 epitopes restricted by 21 different HLA-A (86 epitopes), 46 HLA-B (161 epitopes) and 15 HLA-C (25 epitopes) alleles in 2012. The present update adds an additional 41 epitopes to this list (7 on HLA-A, 29 on HLA-B and 5 on HLA-C alleles with many restricted by traditionally understudied HLA class I alleles. The importance of defining the restricting HLA allele at a 4 digit resolution is highlighted in a number of recent studies that show that the presented epitope repertoires can vary widely even between closely related HLA class I alleles [Kloverpris *et al.*, 2012a,b]. This is especially marked for the HLA-B15 serotype and its subtypes [Frahm *et al.*, 2005, 2006], but is also relevant for other serotypes, for instance HLA-A68, where subtypes fall into different HLA supertypes (A*6801 in A3, A*6802 in A2) and have vastly different HLA binding motifs [Sidney *et al.*, 2008].

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HLA restriction

Based on technical advances in detecting epitope-specific immune response, data on structural characteristics of epitope/HLA complexes and the increasing reliability of known allele-specific binding motifs, we have revised our criteria for inclusion of epitopes in the current issue of the CTL epitopes A-list. Initially, restriction analyses using partly HLA-matched antigen presenting cells covering all 6 classical HLA class I alleles were considered the gold-standard for inclusion of epitopes, owing to the fact that conflicting data were obtained when studying widely promiscuous epitopes. In addition, in early reports, HLA-C alleles were often not typed and not controlled for in restriction analyses. With the improved understanding of the promiscuous nature of CTL epitopes [Frahm *et al.*, 2007], revised definitions of HLA supertypes [Sidney *et al.*, 2008], and the availability of cell lines expressing a single HLA allele, this inclusion criterion is now relaxed. Furthermore, with the advent of tetramer and related technology, the need for extensive cellular HLA-mismatch analyses has been further reduced. As a consequence, the most recent updates of this A-list have increasingly included epitopes for which HLA restriction had been demonstrated by any of the following approaches: single allele expressing cell lines, tetramers, and the older technology of using HLA-mismatched antigen presenting cells, or by inference of peptide binding motifs from closely related HLA alleles. However, we still exclude the predicted HLA restrictions based on large-cohort screenings in which individuals with a matching peptide-specific response share a single, presumably restricting, HLA allele [Kiepiela *et al.*, 2004]. The main reason not to accept such HLA restriction information for the present listing is that it is not uncommon that the emerging alleles are expressed in strong linkage disequilibrium with additional allele(s), making it necessary to experimentally identify the actual restricting allele. While in cases of overwhelming statistical significance (*e.g.*, $p < 10^{-26}$, [Ngumbela *et al.*, 2008]) the predicted HLA would quite likely be correct, it would be problematic to define a cut-off at which a statistically-inferred HLA restriction would be considered sufficient.

Optimal epitope length

When we collected epitopes for the very first A-list of optimal CTL epitopes, we focused strongly on defining an optimal epitope length, which was defined as the shortest peptide eliciting the maximal response. As a consequence, the epitopes that have been included over the years likely reflect more a listing of “minimal” epitopes, not in all cases being the same as the most potent epitope or the one that actually gets presented upon natural antigen processing. This may have led to shorter epitopes being over-represented in the present listing, at the cost of extended epitope variants.

In light of a number of reports showing the existence of longer and bulged epitopes presented by many HLA class I alleles [Burrows *et al.*, 2006; Tenzer *et al.*, 2009], we have now revised our inclusion criteria for new epitopes to be included. For the present update, we have re-examined all epitope entries in the “B-list” of the immunology database (*i.e.*, all reports describing specific T-cell targets in the HIV proteome since 1991) that were of up to 14 amino acids in length for potential well-defined epitopes fulfilling the revised criteria. We have thereby also paid special attention to more recent reports that complement original studies that included incompletely characterized epitopes. This is, for instance, the case where older papers did not include a full set of well-designed peptide truncations, but more recent reports completed them. In some of these cases, we have used published data on escape mutation analyses that cover mutations within and outside the putative optimal epitope. If mutations impact the *in vitro* recognition of the epitopes by specific T cells, it is quite conceivable that the mutation is located within the presented epitope and will reveal the true epitope length, unless the tested variant represents a processing escape mutation. Furthermore, in most cases, titration analyses show marked differences between serially truncated epitope versions, allowing a correct definition of the necessary N- and C-terminal residues.

Conflicting results between laboratories

From our review of the literature, truncation of one amino acid at the N-terminus often conserves CTL recognition, which can evidently lead to a conflicting definition of the optimal epitope length. There are many examples of this, such as the (D)YVDRFFKTL epitope restricted by HLA-Cw*0304 [Kiepiela *et al.*, 2004] or the HLA-Cw*0801 restricted Nef epitope (K)AAVDLSHFL. Such shorter embedded epitopes could still fit the necessary binding requirements for the presenting allele, while other cases may clash with described anchor motifs and indicate that one or the other epitope is likely the naturally produced and presented one. One such example is the well-described HLA-A11 epitope (A)CQGVGGPGHK in Gag-p24 [Sipsas *et al.*, 1997]. The originally reported epitope contains an alanine residue at the N-terminus, making the cysteine the unlikely anchor position for the B-pocket of HLA-A11. Indeed, a more recent report described the optimal epitope as the 10-mer CQGVGGPGHK, although without conducting any truncation analyses [Gong *et al.*, 2006]. Yet, the 10-mer fits the motif with Q in the second position and was used to form highly stable tetramers, strongly suggesting that this is the naturally presented epitope (although truncated versions of original 11-mer epitopes can still form stable tetramers [Propato *et al.*, 2001]). Elution studies are currently under way to identify the actually presented epitope in this case, and similar analyses may be needed to resolve the conflicting data for other epitopes. Finally, dif-

ferent HIV infected subjects mount responses of variable T-cell receptor usage, even if the specific T-cell population may be characterized by a shared variable segment, adding further potential for discrepancies between laboratories using different patient samples [Almeida *et al.*, 2007; Berger *et al.*, 2011].

I-A-3 Revising the criteria for epitope inclusion to the A-list

Despite the above-mentioned potential sources for conflicting data, we have taken following revised criteria for the A-list:

HLA restriction

1. Conclusive HLA restriction analyses, either using a single HLA allele or partly HLA matched antigen-presenting cell lines. To facilitate some of the experimental work, we have generated a set of close to 100 HLA-A, -B and -C expressing plasmids and single allele expressing cell lines, which can be requested from our laboratory.
2. Definition of HLA restriction by tetramer staining or related technology (pentamer, dimer, etc.). Peptide binding to the specific HLA molecule alone is not considered enough evidence that an antigen presenting cell will present the epitope in question on the putative HLA class I molecule. In addition, epitopes that do seem to form tetramers and stain some T cells by flow-cytometry, but which violate existing binding motif information, will require additional experimental demonstration of HLA restriction.
3. We have included some epitopes that were shown by any of the above analyses to be presented by a supertype-matched allele and to fulfill the binding motif of the allele in question and bind it with a $SD_{50\%} < 500$ nM, even though no further HLA restriction analyses were conducted.
4. HLA restriction by elution studies of presented epitopes of single HLA allele expressing antigen presenting cells.

Epitope length

The parameters for epitope length are more difficult to define as the literature has shown multiple instances of embedded/extended epitopes being presented by the same HLA molecule. As a minimum, we encourage the following:

1. Serially truncated *and* extended epitopes around the putative optimal epitope should be tested in peptide titrations assays. If the strongest length variant fulfills the known binding motif, this likely represents the epitope actually presented.

2. Cell free peptide binding studies to the restricting HLA molecule using extended and embedded epitope versions.
3. Structural analyses of epitopes in the context of the presenting HLA molecule.
4. In cases where truncation analyses indicate that more than one length variant is equally well recognized, cross-reactivity studies should be conducted to see whether these populations are cross-reactive or whether individual populations are involved in their recognition. If the latter is the case, both length versions of the epitope will be listed.
5. Definition of epitope length by elution studies of presented epitopes of single HLA allele expressing antigen presenting cells.

From the exhaustive re-examination of the literature that we conducted for this update, it is clear that there are many more already-described epitopes that are quite likely representing “optimal” epitopes, but do not satisfy some of the above criteria. Among these are epitopes identified by binding motif prediction approaches. However, as the present list of experimentally defined epitopes can also serve as training set for binding motif prediction algorithms, we specifically exclude epitopes solely defined based on HLA allele-specific motif predictions, as this would cause the prediction algorithms to be fed with predicted motif information, which tends to return predominantly shorter epitopes [Burrows *et al.*, 2006].

I-A-4 Summary

Careful definition of optimal epitopes can have far reaching consequences for HIV vaccine selection, measurement of host immunity to natural infection, and interpretation of HIV evolution in response to host immune control. The 2013 update of the Los Alamos HIV Immunology Database CTL epitope A-list expands the number of well-described, experimentally fine-mapped and HLA class I restricted epitopes to more than 300, presented across more than 80 different HLA class I alleles. With the increased description of extended and embedded epitopes, however, there is also be a chance that conflicting information on epitope length and HLA restrictions will emerge from different laboratories. We would like to encourage everyone in the field to please communicate these instances, as well as any other gross or less evident mistakes that may still exist in the current listing, so we can correct and annotate listed epitopes accordingly. We again thank all investigators who have contributed to the current listing with unpublished data, suggestions, and questions, which have helped make this listing increasingly useful and accurate.

I-A-5 Table of optimal HIV-1 CTL epitopes

Table I-A-1: Best defined HIV CTL epitopes.

HLA	Protein	AA	Sequence	Reference
A*0101 (A1)	gp160	787–795	RRGWEVLKY	Cao, 2002
A2	RT	127–135	YTAFTIPSV	Draenert <i>et al.</i> , 2006
A*0201 (A2)	p17	77–85	SLYNTVATL	Johnson <i>et al.</i> , 1991; Parker <i>et al.</i> , 1992, 1994
A*0201 (A2)	p17	77–86	SLFNTVATLY	Tenzer <i>et al.</i> , 2009
A*0201 (A2)	p2p7p1p6	70–79	FLGKIWPSYK	Yu <i>et al.</i> , 2002b
A*0201 (A2)	Protease	76–84	LVGPTPVNI	Konya <i>et al.</i> , 1997
A*0201 (A2)	RT	33–41	ALVEICTEM	Haas <i>et al.</i> , 1998; Haas, 1999
A*0201 (A2)	RT	179–187	VIYQYMDL	Harrer <i>et al.</i> , 1996a
A*0201 (A2)	RT	309–317	ILKEPVHGV	Walker <i>et al.</i> , 1989; Tsomides <i>et al.</i> , 1991
A*0201 (A2)	Vpr	59–67	AIIRILQQL	Altfeld <i>et al.</i> , 2001a,b
A*0201 (A2)	gp160	311–320	RGPGRAFVTI	Alexander-Miller <i>et al.</i> , 1996
A*0201 (A2)	gp160	813–822	SLLNATDIAV	Dupuis <i>et al.</i> , 1995
A*0201 (A2)	gp160	814–822	LLNATDIAV	Dupuis <i>et al.</i> , 1995; Brander & Walker, 1995
A*0201 (A2)	Nef	136–145	PLTFGWCYKL	Haas <i>et al.</i> , 1996; Maier & Autran, 1999
A*0201 (A2)	Nef	180–189	VLEWRFDLRL	Haas <i>et al.</i> , 1996; Maier & Autran, 1999
A*0202 (A2)	p17	77–85	SLYNTVATL	Goulder, 1999
A*0205 (A2)	p17	77–85	SLYNTVATL	Goulder, 1999
A*0205 (A2)	gp160	846–854	RIRQLERA	Sabbaj <i>et al.</i> , 2003
A*0205 (A2)	Nef	83–91	GAFDLSFFL	Rathod, 2006
A*0207 (A2)	p24	164–172	YVDRFYKTL	Currier <i>et al.</i> , 2002
A*0301 (A3)	p17	18–26	KIRLRPGGK	Harrer <i>et al.</i> , 1996b
A*0301 (A3)	p17	20–28	RLRPGGKCK	Goulder <i>et al.</i> , 1997b; Culmann, 1999; Lewinsohn & Riddell, 1999; Wilkes & Ruhl, 1999
A*0301 (A3)	p17	20–29	RLRPGGKKKY	Goulder <i>et al.</i> , 2000b
A*0301 (A3)	RT	33–43	ALVEICTEMEK	Haas <i>et al.</i> , 1998; Haas, 1999
A*0301 (A3)	RT	73–82	KLVDLFRELNK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	RT	93–101	GIPHPAGLK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	RT	158–166	AIFQSSMTK	Threlkeld <i>et al.</i> , 1997
A*0301 (A3)	RT	269–277	QIYPGIKVR	Yu <i>et al.</i> , 2002a
A*0301 (A3)	RT	356–366	RMRGAHTNDVK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Integrase	179–188	AVFIHNFKRK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Vif	17–26	RIRTWKSLVK	Altfeld <i>et al.</i> , 2001a; Yu <i>et al.</i> , 2002a
A*0301 (A3)	Vif	28–36	HMYISKKAK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Vif	158–168	KTKPPLPSVKK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Rev	57–66	ERILSTYLGR	Addo, 2002; Yu <i>et al.</i> , 2002a
A*0301 (A3)	gp160	37–46	TVYYGVPVWK	Johnson <i>et al.</i> , 1994
A*0301 (A3)	gp160	770–780	RLRDLLIVTR	Takahashi <i>et al.</i> , 1991
A*0301 (A3)	Nef	73–82	QVPLRPMYTK	Koenig <i>et al.</i> , 1990; Culmann <i>et al.</i> , 1991
A*0301 (A3)	Nef	84–92	AVDLSHFLK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Cryptic		RTSKASLER	Berger <i>et al.</i> , 2010 frameshifted Pol 236–244

Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
A11	Integrase	203–211	IIATDIQTK	Wang <i>et al.</i> , 2007
A*1101 (A11)	p17	84–91	TLYCVHQK	Harrer <i>et al.</i> , 1998
A*1101 (A11)	p24	217–227	ACQGVGGPGHK	Sipsas <i>et al.</i> , 1997
A*1101 (A11)	RT	158–166	AIFQSSMTK	Johnson & Walker, 1994; Zhang <i>et al.</i> , 1993; Threlkeld <i>et al.</i> , 1997
A*1101 (A11)	RT	341–350	IYQEPFKNLK	Culmann, 1999
A*1101 (A11)	RT	520–528	QIIEQLIKK	Fukada <i>et al.</i> , 1999
A*1101 (A11)	Integrase	179–188	AVFIHNFKRK	Fukada <i>et al.</i> , 1999
A*1101 (A11)	gp160	199–207	SVITQACPK	Fukada <i>et al.</i> , 1999
A*1101 (A11)	Nef	73–82	QVPLRPMTYK	Buseyne, 1999
A*1101 (A11)	Nef	75–82	PLRPMTYK	Culmann <i>et al.</i> , 1991
A*1101 (A11)	Nef	84–92	AVDLSHFLK	Culmann <i>et al.</i> , 1991
A23	gp160	585–593	RYLKDQQLL	Cao <i>et al.</i> , 2003
A*2402 (A24)	p17	28–36	KYKCLKHIVW	Ikeda-Moore <i>et al.</i> , 1998; Lewinsohn, 1999
A*2402 (A24)	p24	162–172	RDYVDRFFKTL	Dorrell <i>et al.</i> , 1999; Rowland-Jones, 1999
A*2402 (A24)	gp160	52–61	LFCASDAKAY	Lieberman <i>et al.</i> , 1992; Shankar <i>et al.</i> , 1996
A*2402 (A24)	gp160	585–593	RYLKDQQLL	Dai <i>et al.</i> , 1992
A*2402 (A24)	Nef	134–141	RYPLTFGW	Goulder <i>et al.</i> , 1997a; Ikeda-Moore <i>et al.</i> , 1998
A*2501 (A25)	p24	13–23	QAISPRTLNAW	Kurane & West, 1999
A*2501 (A25)	p24	71–80	ETINEEAAEW	Klenerman <i>et al.</i> , 1996; van Baalen <i>et al.</i> , 1996
A*2501 (A25)	gp160	321–330	EIIGDIRQAY	Liu <i>et al.</i> , 2006
A*2601 (A26)	p24	35–43	EVIPMFSAL	Goulder <i>et al.</i> , 1996a
A*2601 (A26)	RT	449–457	ETKLGKAGY	Sabbaj <i>et al.</i> , 2003
A*2602 (A26)	p24	35–43	EVIPMFSAL	Kawashima <i>et al.</i> , 2008
A*2603 (A26)	p24	35–43	EVIPMFSAL	Kawashima <i>et al.</i> , 2008
A29	Nef	120–128	YFPDWQNYT	Draenert <i>et al.</i> , 2004a
A*2902 (A29)	p17	78–86	LYNTVATLY	Masemola <i>et al.</i> , 2004
A*2902 (A29)	gp160	209–217	SFEPIPIHY	Altfeld, 2000
A30	p17	34–44	LVWASRELERF	Masemola <i>et al.</i> , 2004
A*3002 (A30)	p17	76–86	RSLYNTVATLY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	RT	173–181	KQNPDIYIY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	RT	263–271	KLNWASQIY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	RT	356–365	RMRGAHTNDV	Sabbaj <i>et al.</i> , 2003
A*3002 (A30)	Integrase	219–227	KIQNFRVYY	Sabbaj <i>et al.</i> , 2003; Rodriguez <i>et al.</i> , 2004
A*3002 (A30)	gp160	310–318	HIGPGRAFY	Sabbaj <i>et al.</i> , 2003
A*3002 (A30)	gp160	704–712	IVNRRQGY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	gp160	794–802	KYCWNLLQY	Goulder <i>et al.</i> , 2001
A*3101 (A31)	gp160	770–780	RLRDLILLIVTR	Safrit <i>et al.</i> , 1994a,b
A*3201 (A32)	RT	392–401	PIQKETWETW	Harrer <i>et al.</i> , 1996b
A*3201 (A32)	gp160	419–427	RIKQIINMW	Harrer <i>et al.</i> , 1996b

Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
A33	Nef	133–141	TRYPLTFGW	Cao, 2002
A*3303 (A33)	Vpu	29–37	EYRKILRQR	Addo <i>et al.</i> , 2002
A*3303 (A33)	gp160	698–707	VFAVLSIVNR	Hossain <i>et al.</i> , 2001
A*3303 (A33)	gp160	831–838	EVAQRAYR	Hossain <i>et al.</i> , 2001
A66	RT	438–448	ETFYVDGAANR	Rathod, 2006
A*6801 (A68)	Vpr	52–62	DTWAGVEAIR	Sabbaj <i>et al.</i> , 2004
A*6801 (A68)	Tat	39–49	ITKGLGISYGR	Oxenius <i>et al.</i> , 2002
A*6802 (A68)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999
A*6802 (A68)	Protease	30–38	DTVLEEWNL	Rowland-Jones, 1999
A*6802 (A68)	RT	436–445	GAETFYVDGA	Rathod & Kiepiela, 2005
A*6802 (A68)	Vpr	48–57	ETYGDTWTGV	Rathod & Kiepiela, 2005
A*6802 (A68)	gp160	777–785	IVTRIVELL	Wilkes, 1999
A*7401 (A19)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999
B7	p24	84–92	HPVHAGPIA	Yu <i>et al.</i> , 2002a; Westrop <i>et al.</i> , 2009
B7	RT	156–164	SPAIFQSSM	Linde & Faircloth, 2006
B7	Rev	66–75	RPAEPVPLQL	Yang, 2006
B*0702 (B7)	p24	16–24	SPRTLNAWV	Lewinsohn, 1999
B*0702 (B7)	p24	48–56	TPQDLNTML	Wilson, 1999; Wilkes <i>et al.</i> , 1999; Jin <i>et al.</i> , 2000; Wilson <i>et al.</i> , 1997
B*0702 (B7)	p24	223–231	GPGHKARVL	Goulder, 1999
B*0702 (B7)	Vpr	34–42	FPRIWLHGL	Altfeld <i>et al.</i> , 2001a
B*0702 (B7)	Vif	48–57	HPRVSSEVHI	Altfeld <i>et al.</i> , 2001a
B*0702 (B7)	gp160	298–307	RPNNNTRKSI	Safrit <i>et al.</i> , 1994b
B*0702 (B7)	gp160	843–851	IPRRIRQGL	Wilkes & Ruhl, 1999
B*0702 (B7)	Nef	68–77	FPVTPQVPLR	Haas <i>et al.</i> , 1996; Maier & Autran, 1999
B*0702 (B7)	Nef	68–76	FPVTPQVPL	Bauer <i>et al.</i> , 1997; Frahm & Goulder, 2002
B*0702 (B7)	Nef	71–79	TPQVPLRPM	Goulder, 1999
B*0702 (B7)	Nef	77–85	RPMTYKAAL	Bauer <i>et al.</i> , 1997
B*0702 (B7)	Nef	128–137	TPGPGVRYPL	Culmann-Penciolelli <i>et al.</i> , 1994; Haas <i>et al.</i> , 1996
B8	gp160	848–856	RQGLERALL	Cao, 2002
B*0801 (B8)	p17	24–32	GGKKKYKLLK	Reid <i>et al.</i> , 1996; Goulder <i>et al.</i> , 1997d
B*0801 (B8)	p17	74–82	ELRSLYNTV	Goulder <i>et al.</i> , 1997d
B*0801 (B8)	p24	128–135	EIYKRWII	Sutton <i>et al.</i> , 1993; Goulder <i>et al.</i> , 1997d
B*0801 (B8)	p24	197–205	DCKTILKAL	Sutton <i>et al.</i> , 1993
B*0801 (B8)	RT	18–26	GPKVKQWPL	Walker <i>et al.</i> , 1989; Sutton <i>et al.</i> , 1993
B*0801 (B8)	gp160	2–10	RVKEYQHL	Sipsas <i>et al.</i> , 1997
B*0801 (B8)	gp160	586–593	YLKDQQLL	Johnson <i>et al.</i> , 1992; Shankar <i>et al.</i> , 1996
B*0801 (B8)	Nef	13–20	WPTVRERM	Goulder <i>et al.</i> , 1997d
B*0801 (B8)	Nef	90–97	FLKEKGGL	Culmann-Penciolelli <i>et al.</i> , 1994; Price <i>et al.</i> , 1997

Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B13	p24	3–11	VQNLQGQMV	Honeyborne <i>et al.</i> , 2007
B13	p24	94–104	GQMREPRGSDI	Honeyborne <i>et al.</i> , 2007
B13	p2p7p1p6	66–74	RQANFLGKI	Honeyborne <i>et al.</i> , 2007
B13	Protease	57–66	RQYDQILIEI	Honeyborne <i>et al.</i> , 2007; Mueller <i>et al.</i> , 2007
B13	RT	333–341	GQGQWYQI	Honeyborne <i>et al.</i> , 2007
B13	Nef	106–114	RQDILDLWI	Harrer <i>et al.</i> , 2005; Honeyborne <i>et al.</i> , 2007
B*1302 (B13)	Nef	106–114	RQDILDLVV	Gray <i>et al.</i> , 2009
B14	p2p7p1p6	42–50	CRAPRKKGC	Yu <i>et al.</i> , 2002b
B*1401 (B14)	RT	142–149	IRYQYNVL	Rathod, 2006
B*1402 (B14)	p24	166–174	DRFYKTLRA	Harrer <i>et al.</i> , 1996b
B*1402 (B14)	gp160	584–592	ERYLKDQQL	Johnson <i>et al.</i> , 1992
B*1501 (B62)	p24	137–145	GLNKIVRMV	Johnson <i>et al.</i> , 1991; Goulder, 1999
B*1501 (B62)	RT	260–271	LVGKLNWASQIY	Johnson, 1999
B*1501 (B62)	RT	309–318	ILKEPVHGVY	Johnson <i>et al.</i> , 1991; Johnson, 1999
B*1501 (B62)	Nef	117–127	TQGYFPDWQNY	Culmann, 1999
B*1503 (B72)	p24	24–32	VKVIEEKAF	Honeyborne & Kiepiela, 2005
B*1503 (B72)	p24	164–172	YVDRFFKTL	Masemola <i>et al.</i> , 2004
B*1503 (B72)	Protease	68–76	GKKAIGTVL	Rathod & Bishop, 2006
B*1503 (B72)	RT	496–505	VTDSQYALGI	Sabbaj <i>et al.</i> , 2003
B*1503 (B72)	Integrase	135–143	IQQEFQIPY	Honeyborne & Kiepiela, 2005
B*1503 (B72)	Integrase	185–194	FKRKGIGGY	Honeyborne, 2003
B*1503 (B72)	Integrase	263–271	RKAKIIRDY	Cao <i>et al.</i> , 2003
B*1503 (B72)	Tat	38–47	FQTKGLGISY	Novitsky <i>et al.</i> , 2001
B*1503 (B72)	Nef	183–191	WRFDSRLAF	Cao, 2002
B*1510 (B71)	p24	12–20	HQAISPRTL	Day, 2005
B*1510 (B71)	p24	61–69	GHQAAMQML	Day, 2003
B*1510 (B71)	Integrase	66–74	THLEGKIIL	Kiepiela <i>et al.</i> , 2007
B*1510 (B71)	Vif	79–87	WHLGHGYSI	Honeyborne, 2003
B*1516 (B63)	gp160	375–383	SFNCGGEFF	Wilson <i>et al.</i> , 1997; Wilson, 1999
B18	RT	137–146	NETPGIRYQY	Rathod & Bishop, 2006
B18	RT	175–183	NPEIVYQY	Rathod, 2006
B18	Nef	105–115	RRQDILDLVVY	Yang, 2006
B*1801 (B18)	p24	161–170	FRDYVDRFYK	Ogg <i>et al.</i> , 1998
B*1801 (B18)	Vif	102–111	LADQLIHLHY	Altfeld <i>et al.</i> , 2001a
B*1801 (B18)	gp160	31–39	AENLWTVY	Liu <i>et al.</i> , 2006
B*1801 (B18)	gp160	61–69	YETEVHNVW	Liu <i>et al.</i> , 2006
B*1801 (B18)	Nef	135–143	YPLTFGWY	Culmann <i>et al.</i> , 1991; Culmann-Penciolelli <i>et al.</i> , 1994

Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B27	Vpr	31–39	VRHFPRIWL	Addo & Rathod, 2004
B*2703 (B27)	p24	131–140	RRWIQLGLQK	Rowland-Jones <i>et al.</i> , 1998; Rowland-Jones, 1999
B*2703 (B27)	Nef	76–84	LRPMTYKAA	Huang <i>et al.</i> , 2010
B*2705 (B27)	p17	19–27	IRLRPGGKK	McKinney <i>et al.</i> , 1999; Lewinsohn, 1999
B*2705 (B27)	p24	131–140	KRWIILGLNK	Nixon <i>et al.</i> , 1988; Buseyne <i>et al.</i> , 1993; Goulder <i>et al.</i> , 1997c
B*2705 (B27)	Integrase	186–194	KRKGIGGY	Payne & Goulder, 2009
B*2705 (B27)	gp160	786–795	GRRGWEALKY	Lieberman <i>et al.</i> , 1992; Lieberman, 1999
B*2705 (B27)	Nef	105–114	RRQIDLWLI	Goulder <i>et al.</i> , 1997b
B35	Nef	71–81	RPQVPLRPMTY	Motozono <i>et al.</i> , 2009
B*3501 (B35)	p17	36–44	WASRELERF	Goulder <i>et al.</i> , 1997a
B*3501 (B35)	p17	124–132	NSSKVSQNY	Rowland-Jones <i>et al.</i> , 1995
B*3501 (B35)	p24	84–92	HPVHAGPIA	Westrop <i>et al.</i> , 2009; Matthews <i>et al.</i> , 2012
B*3501 (B35)	p24	121–130	NPPIPVGDYI	Matthews <i>et al.</i> , 2012
B*3501 (B35)	p24	122–130	PPIPVGDIY	Rowland-Jones <i>et al.</i> , 1995
B*3501 (B35)	RT	107–115	TVLDVGDY	Wilkes & Ruhl, 1999; Wilson <i>et al.</i> , 1999
B*3501 (B35)	RT	118–127	VPLDEFKRY	Sipsas <i>et al.</i> , 1997; Shiga <i>et al.</i> , 1996
B*3501 (B35)	RT	175–183	HPDIVIYQY	Rowland-Jones <i>et al.</i> , 1995; Shiga <i>et al.</i> , 1996; Sipsas <i>et al.</i> , 1997
B*3501 (B35)	RT	293–301	IPLTEEAEL	Tomiyama <i>et al.</i> , 2000
B*3501 (B35)	gp160	42–52	VPVWKEATTTL	Wilkes & Ruhl, 1999
B*3501 (B35)	gp160	78–86	DPNPQEVVL	Shiga <i>et al.</i> , 1996
B*3501 (B35)	gp160	606–614	TAVPWNASW	Johnson <i>et al.</i> , 1994
B*3501 (B35)	Nef	74–81	VPLRPMTY	Culmann <i>et al.</i> , 1991; Culmann-Penciolelli <i>et al.</i> , 1994
B*3501 (B35)	Nef	120–128	YFPDWQNYT	Frahm <i>et al.</i> , 2007
B*3701 (B37)	Nef	120–128	YFPDWQNYT	Culmann <i>et al.</i> , 1991; Culmann, 1999
B*3801 (B38)	Vif	79–87	WHLGQGVSI	Sabbaj <i>et al.</i> , 2004
B*3801 (B38)	gp160	104–112	MHEDIISLW	Cao, 2002
B*3901 (B39)	p24	61–69	GHQAAMQML	Kurane & West, 1999
B*3910 (B39)	p24	48–56	TPQDLNTML	Honeyborne & Kiepiela, 2005
B*4001 (B60)	p17	92–101	IEIKDTKEAL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	p24	44–52	SEGATPQDL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	p2p7p1p6	118–126	KELYPLTSL	Yu <i>et al.</i> , 2002b
B*4001 (B60)	RT	5–12	IETVPVKL	Draenert <i>et al.</i> , 2004b
B*4001 (B60)	RT	202–210	IEELRQHLL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	gp160	805–814	QELKNSAVSL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	Nef	37–45	LEKHGAITS	Draenert <i>et al.</i> , 2004b
B*4001 (B60)	Nef	92–100	KEKGGLEGL	Altfeld <i>et al.</i> , 2000

Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B*4002 (B61)	p17	11–19	GELDRWEKI	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	p24	70–78	KETINEEAA	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	p24	78–86	AEWDRVHPV	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	p2p7p1p6	64–71	TERQANFL	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	Integrase	84–93	IEAEVIPAET	Watanabe <i>et al.</i> , 2011
B*4002 (B61)	Integrase	197–204	GERIVDII	Watanabe <i>et al.</i> , 2011
B*4002 (B61)	Nef	92–100	KEKGGLEGL	Sabbaj <i>et al.</i> , 2003; Altfeld <i>et al.</i> , 2000
B42	Integrase	260–268	VPRRKAKII	Kiepiela & Goulder, 2002
B*4201 (B42)	p24	48–56	TPQDLNTML	Goulder <i>et al.</i> , 2000a
B*4201 (B42)	RT	271–279	YPGIKVRQL	Wilkes & Ruhl, 1999
B*4201 (B42)	Integrase	28–36	LPPIVAKEI	Kiepiela <i>et al.</i> , 2007
B*4201 (B42)	Nef	71–79	RPQVPLRPM	Honeyborne, 2006
B*4201 (B42)	Nef	128–137	TPGPGVRYPL	Goulder, 1999
B*4202 (B42)	Nef	71–79	RPQVPLRPM	Kloverpris <i>et al.</i> , 2012b
B*4202 (B42)	Nef	128–137	TPGPGVRYPL	Kloverpris <i>et al.</i> , 2012b
B44	Protease	34–42	EEMNLPGRW	Rodriguez <i>et al.</i> , 2004
B44	gp160	31–39	AENLWTVY	Borrow <i>et al.</i> , 1997
B*4402 (B44)	p24	162–172	RDYVDRFYKTL	Ogg <i>et al.</i> , 1998
B*4402 (B44)	p24	174–184	AEQASQDVKNW	Lewinsohn, 1999
B*4402 (B44)	gp160	31–40	AENLWTVYY	Borrow <i>et al.</i> , 1997
B*4403 (B44)	p17	78–86	LYNTVATLY	Masemola <i>et al.</i> , 2004
B*4415 (B12)	p24	28–36	EEKAFSPEV	Bird <i>et al.</i> , 2002
B*4501 (B45)	p2p7p1p6	1–10	AEAMSQVTNS	Sabbaj <i>et al.</i> , 2004
B*4801 (B48)	p24	181–189	VKNWMTETL	Murakoshi <i>et al.</i> , 2009
B*4801 (B48)	p2p7p1p6	66–74	RQANFLGKI	Murakoshi <i>et al.</i> , 2009
B50	Nef	37–45	LEKHGAITS	Draenert <i>et al.</i> , 2004b
B51	Vif	57–66	IPLGDAKLII	Bansal <i>et al.</i> , 2004
B51	Vpr	29–37	EAVRHFPRI	Cao <i>et al.</i> , 2003
B*5101 (B51)	p17	22–31	RPGGKKKYKL	Huang <i>et al.</i> , 2010
B*5101 (B51)	RT	128–135	TAFTIPSI	Sipsas <i>et al.</i> , 1997
B*5101 (B51)	RT	293–301	IPLTEEAEL	Tomiyama <i>et al.</i> , 2000
B*5101 (B51)	gp160	416–424	LPCRKQII	Tomiyama <i>et al.</i> , 1999
B*5201 (B52)	p24	143–150	RMYSPTSI	Wilkes & Ruhl, 1999; Wilson <i>et al.</i> , 1997
B53	p24	48–56	TPQDLNML	Dorrell <i>et al.</i> , 2001
B53	Nef	135–143	YPLTFGWCF	Kiepiela & Goulder, 2002
B*5301 (B53)	p24	48–56	TPYDINQML	Gotch <i>et al.</i> , 1993
B*5301 (B53)	p24	176–184	QASQEVKNW	Buseyne <i>et al.</i> , 1996, 1997; Buseyne, 1999
B*5301 (B53)	Nef	135–143	YPLTFGWCY	Sabbaj <i>et al.</i> , 2003

Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B*5401 (B54)	Protease-RT	99–8	FPISPIETV	Kitano <i>et al.</i> , 2008
B*5401 (B54)	RT	149–158	LPQGWKGSPA	Kitano <i>et al.</i> , 2008
B*5401 (B54)	Integrase	78–86	HVASGYIEA	Kitano <i>et al.</i> , 2008
B*5401 (B54)	Nef	121–129	FPDWQNYTP	Kitano <i>et al.</i> , 2008
B*5501 (B55)	gp160	42–51	VPVWKEATTT	Shankar <i>et al.</i> , 1996; Lieberman, 1999
B57	p24	32–40	FSPEVIPMF	Frahm <i>et al.</i> , 2005
B57	Protease	70–77	KAIGTVLV	Frahm <i>et al.</i> , 2005
B57	Integrase	123–132	STTVKAACWW	Rodriguez <i>et al.</i> , 2004; Addo & Rathod, 2004
B57	Nef	116–124	HTQGYFPDW	Draenert, 2002
B57	Nef	127–135	YTPGPGIRY	Frahm <i>et al.</i> , 2005
B57	Nef	137–145	LTFGWCFKL	Frahm <i>et al.</i> , 2005
B*5701 (B57)	p24	15–23	ISPRTLNAW	Johnson <i>et al.</i> , 1991; Goulder <i>et al.</i> , 1996b
B*5701 (B57)	p24	30–40	KAFSPEVIPMF	Goulder <i>et al.</i> , 1996b
B*5701 (B57)	p24	108–117	TSTLQEQIGW	Goulder <i>et al.</i> , 1996b
B*5701 (B57)	p24	176–184	QASQEVKNW	Goulder <i>et al.</i> , 1996b
B*5701 (B57)	RT	244–252	IVLPEKDSW	van der Burg <i>et al.</i> , 1997; Hay, 1999
B*5701 (B57)	Integrase	173–181	KTAVQMAVF	Goulder <i>et al.</i> , 1996b; Hay, 1999
B*5701 (B57)	Vif	31–39	ISKKAKGWF	Altfeld <i>et al.</i> , 2001a
B*5701 (B57)	Vpr	30–38	AVRHFPRIW	Altfeld <i>et al.</i> , 2001a
B*5701 (B57)	Rev	14–23	KAVRLIKFLY	Addo <i>et al.</i> , 2001
B*5703 (B57)	p24	30–37	KAFSPEVI	Goulder <i>et al.</i> , 2000b
B*5703 (B57)	p24	30–40	KAFSPEVIPMF	Goulder <i>et al.</i> , 2000b
B*5703 (B57)	Vif	81–89	LGHGVSIEW	Kløverpris <i>et al.</i> , 2013
B*5703 (B57)	Rev	14–23	QAVRIKILY	Kløverpris <i>et al.</i> , 2013
B*5703 (B57)	Nef	82–90	KAAFDLSFF	Leslie <i>et al.</i> , 2005; Kløverpris <i>et al.</i> , 2012b
B*5703 (B57)	Nef	83–91	AAFDSLFFL	Gray <i>et al.</i> , 2009
B*5703 (B57)	Nef	116–124	HTQGYFPDW	Kløverpris <i>et al.</i> , 2013
B58	p17	76–86	RSLYNTVATLY	Frahm <i>et al.</i> , 2005
B58	gp160	59–69	KAYETEVHNVW	Rathod & Bishop, 2006
B*5801 (B58)	p24	108–117	TSTLQEQIGW	Goulder <i>et al.</i> , 1996b; Bertoletti <i>et al.</i> , 1998
B*5801 (B58)	p24	176–184	QASQEVKNW	Gillespie <i>et al.</i> , 2005; Kløverpris <i>et al.</i> , 2013
B*5801 (B58)	RT	375–383	IAMESIVIW	Kiepiela & Goulder, 2002
B*5801 (B58)	Rev	14–23	KAVRLIKFLY	Addo <i>et al.</i> , 2001
B*5801 (B58)	Nef	82–90	KAAFDLSFF	Leslie <i>et al.</i> , 2005
B*5801 (B58)	Nef	116–124	HTQGYFPDW	Kløverpris <i>et al.</i> , 2013
B*5802 (B58)	gp160	577–587	QTRVLAIERYL	Ngumbela <i>et al.</i> , 2008
B62	p24	137–145	GLNKIVRMV	Goulder <i>et al.</i> , 2000c
B62	Nef	19–27	RMRAEPAA	Cao, 2002
B63	p17	76–86	RSLYNTVATLY	Frahm <i>et al.</i> , 2005
B63	p24	15–23	ISPRTLNAW	Frahm <i>et al.</i> , 2005
B63	p24	30–40	KAFSPEVIPMF	Frahm <i>et al.</i> , 2005
B63	Rev	14–23	KAVRLIKFLY	Frahm <i>et al.</i> , 2005
B63	Nef	127–135	YTPGPGIRY	Frahm <i>et al.</i> , 2005
B63	Nef	137–145	LTFGWCFKL	Frahm <i>et al.</i> , 2005

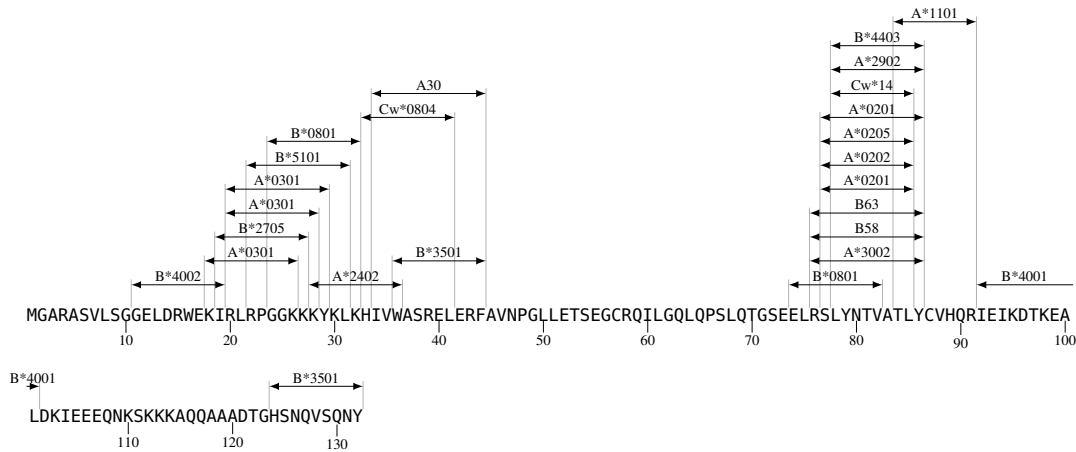
Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B81	Protease	80–90	TPVNIIGRNML	Honeyborne <i>et al.</i> , 2006
B81	RT-Integrase	560–8	LFLDGIDKA	Addo, 2002
B*8101 (B81)	p24	48–56	TPQDLNTML	Goulder <i>et al.</i> , 2000a
B*8101 (B81)	Vpr	34–42	FPRIWLHGL	Altfeld <i>et al.</i> , 2001a
Cw1	gp160	218–226	CAPAGFAIL	Zuñiga, 2008; Streeck <i>et al.</i> , 2008
Cw*0102 (Cw1)	p24	36–43	VIPMFSAL	Goulder <i>et al.</i> , 1997a
Cw*0102 (Cw1)	p24	145–153	YSPVSILDI	Buranapraditkun <i>et al.</i> , 2011
Cw*0102 (Cw1)	Gag-Pol TF	24–31	NSPTRREL	Liu <i>et al.</i> , 2006
Cw3	Nef	83–91	AALDLSHFL	Draenert <i>et al.</i> , 2004b
Cw*0303 (Cw9)	p24	164–172	YVDRFFKTL	Honeyborne, 2003
Cw*0304 (Cw10)	p24	164–172	YVDRFFKTL	Honeyborne, 2003
Cw*0304 (Cw10)	gp160	557–565	RAIEAQQHL	Currier <i>et al.</i> , 2002; Trocha, 2002
Cw*0401 (Cw4)	gp160	375–383	SFNCGGEFF	Wilson <i>et al.</i> , 1997; Johnson <i>et al.</i> , 1993
Cw5	p24	174–185	AEQASQEVKNWM	Draenert <i>et al.</i> , 2004b
Cw5	Integrase	114–121	HTDNGSNF	Brockman <i>et al.</i> , 2012
Cw*0501	Rev	67–75	SAEPVPLQL	Addo <i>et al.</i> , 2001
Cw6	Nef	120–128	YFPDQNYT	Frahm <i>et al.</i> , 2007
Cw7	Nef	105–115	KRQEILDLWVY	Kiepiela & Goulder, 2002; Yu <i>et al.</i> , 2002a
Cw8	gp160	557–565	RAIEAQQHM	Bishop & Honeyborne, 2006
Cw8	Nef	82–91	KAAVDLSHFL	Harrer <i>et al.</i> , 1996b
Cw*0802 (Cw8)	p24	48–56	TPQDLNTML	Goulder <i>et al.</i> , 2000a; Honeyborne & Kiepiela, 2005
Cw*0802 (Cw8)	RT	495–503	IVTDSQYAL	Rathod & Honeyborne, 2006
Cw*0802 (Cw8)	Nef	83–91	AAVDLSHFL	Cao <i>et al.</i> , 2003; Rathod & Honeyborne, 2006
Cw*0804 (Cw8)	p17	33–41	HLVWASREL	Masemola <i>et al.</i> , 2004
Cw12	Tat	30–37	CCFHCQVC	Cao <i>et al.</i> , 2003; Nixon <i>et al.</i> , 1999
Cw*1202 (Cw12)	RT	173–181	KQNPDIYIY	Honda <i>et al.</i> , 2011
Cw*1202 (Cw12)	RT	309–318	ILKEPVHGVY	Honda <i>et al.</i> , 2011
Cw14	p17	78–85	LYNTVATL	Horton & Havenar-Daughton, 2005
Cw15	gp160	557–565	RAIEAQQHL	Trocha, 2002
Cw18	p24	142–150	VRMYSVSI	Honeyborne, 2006
Cw18	p24	161–169	FRDYVDRFF	Honeyborne & Kiepiela, 2005
Cw18	Integrase	165–172	VRDQAEHL	Rathod & Honeyborne, 2006
Cw18	Vpu	5–13	YRLGVGALI	Honeyborne, 2006

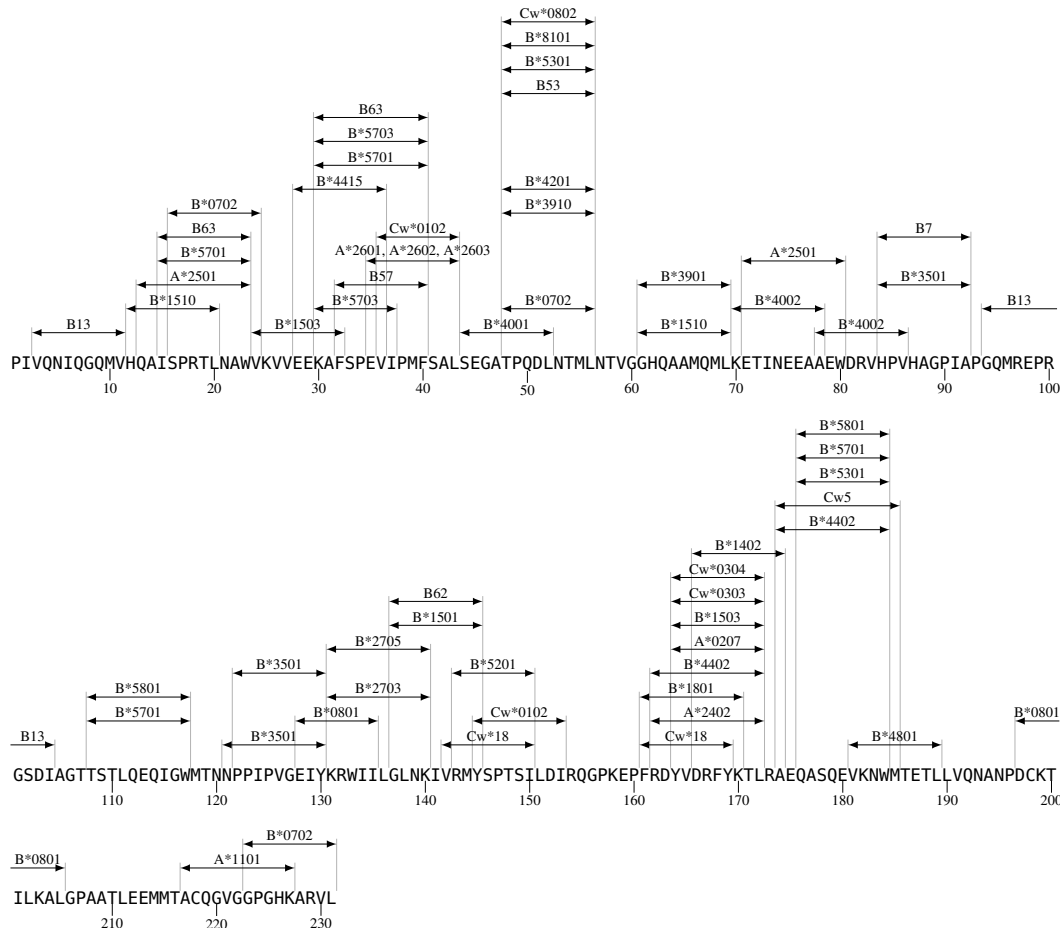
I-A-6 Map of optimal HIV-1 CTL epitopes

The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined.

p17 Optimal CTL Epitope Map

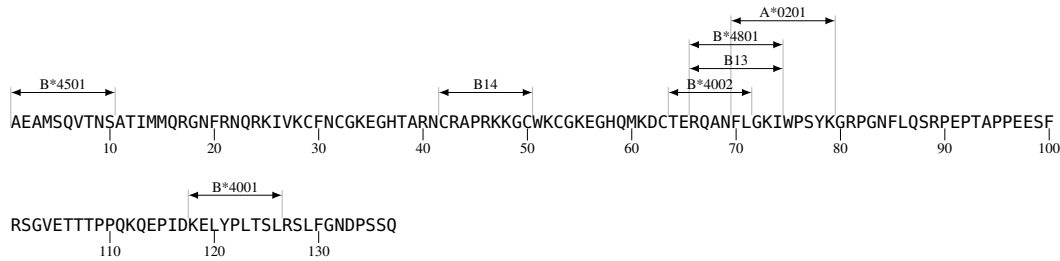


p24 Optimal CTL Epitope Map

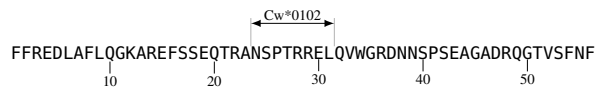


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p2p7p1p6 Optimal CTL Epitope Map



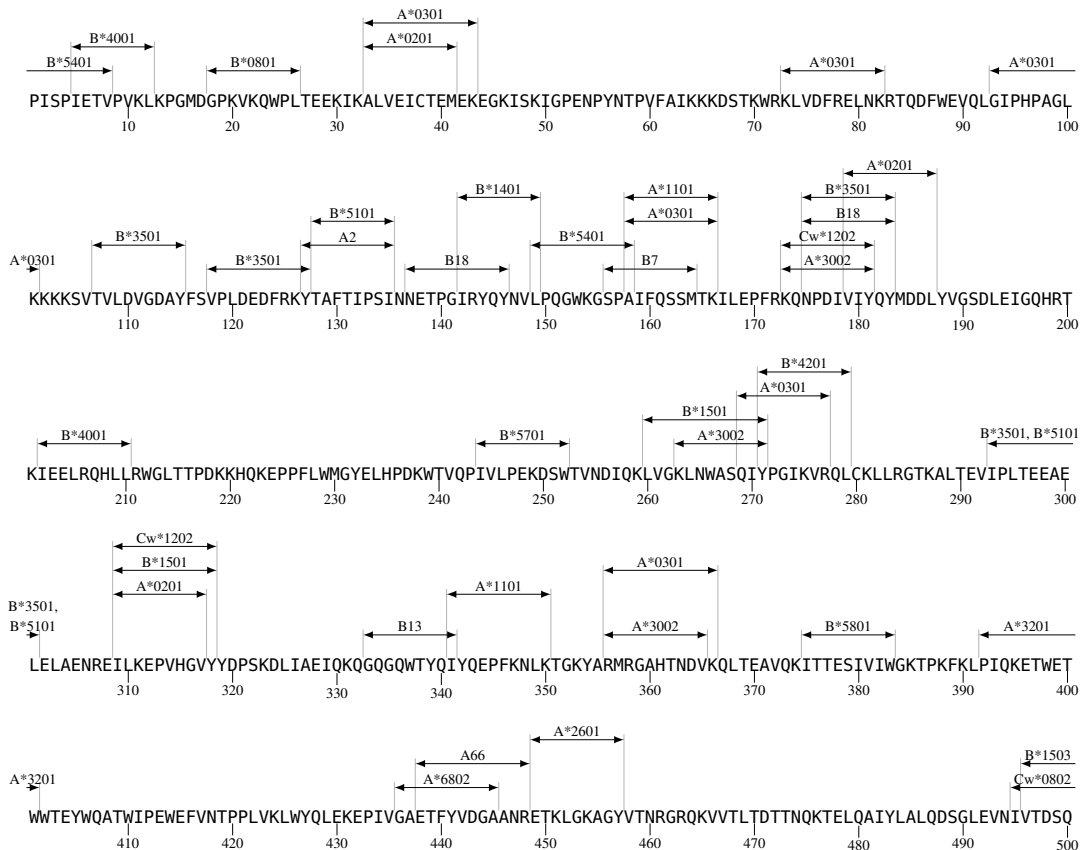
Gag/Pol TF Optimal CTL Epitope Map



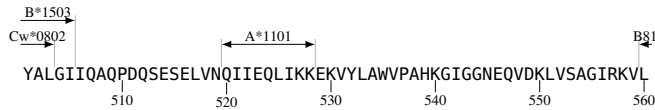
Protease Optimal CTL Epitope Map



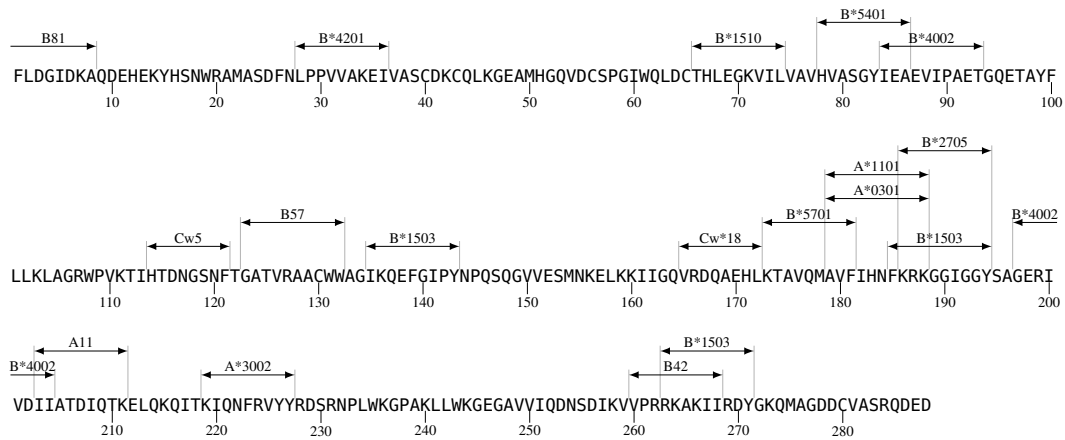
RT Optimal CTL Epitope Map



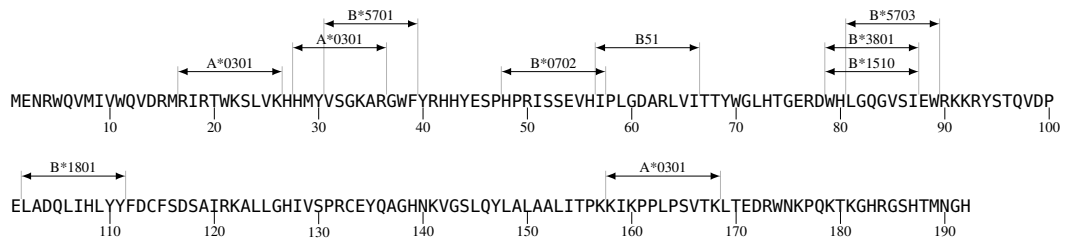
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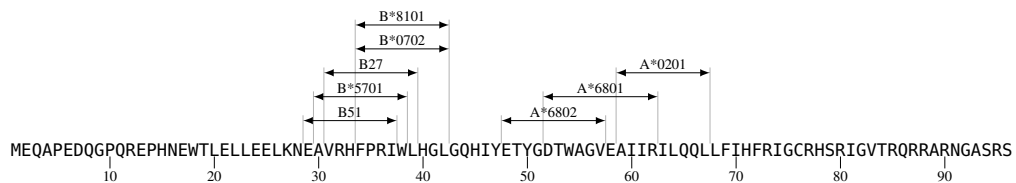
Integrase Optimal CTL Epitope Map



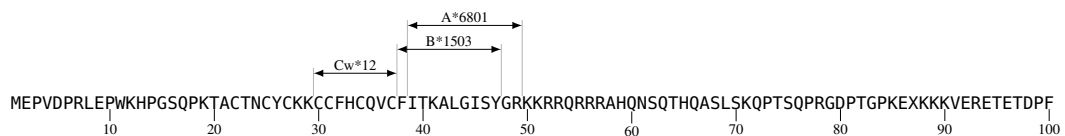
Vif Optimal CTL Epitope Map



Vpr Optimal CTL Epitope Map

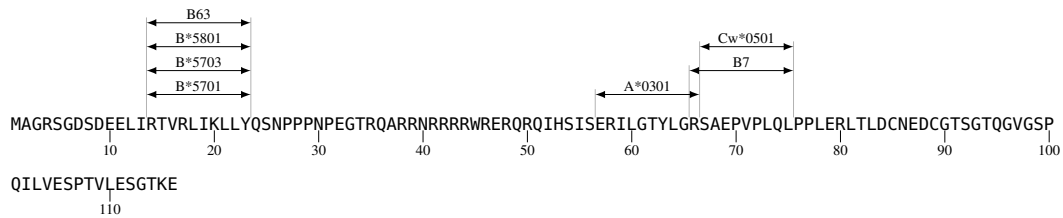


Tat Optimal CTL Epitope Map

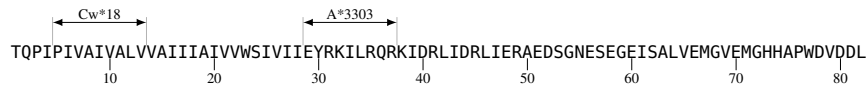


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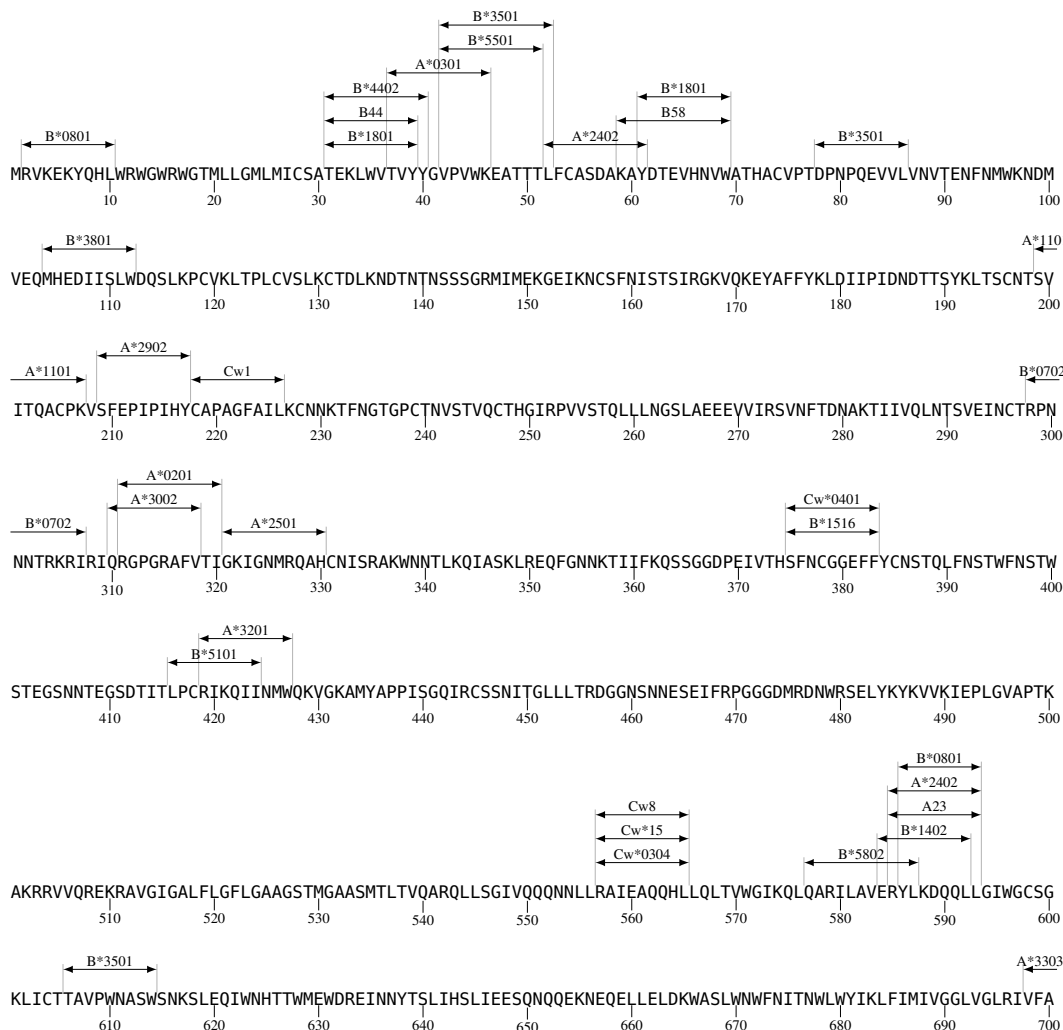
Rev Optimal CTL Epitope Map



Vpu Optimal CTL Epitope Map



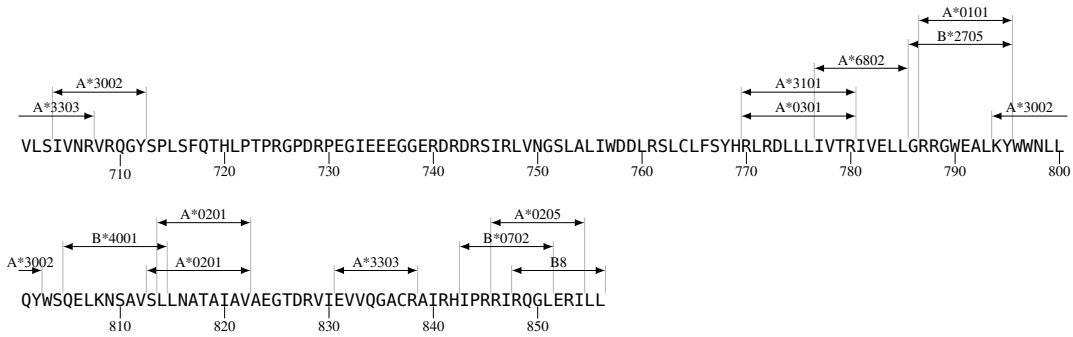
gp160 Optimal CTL Epitope Map



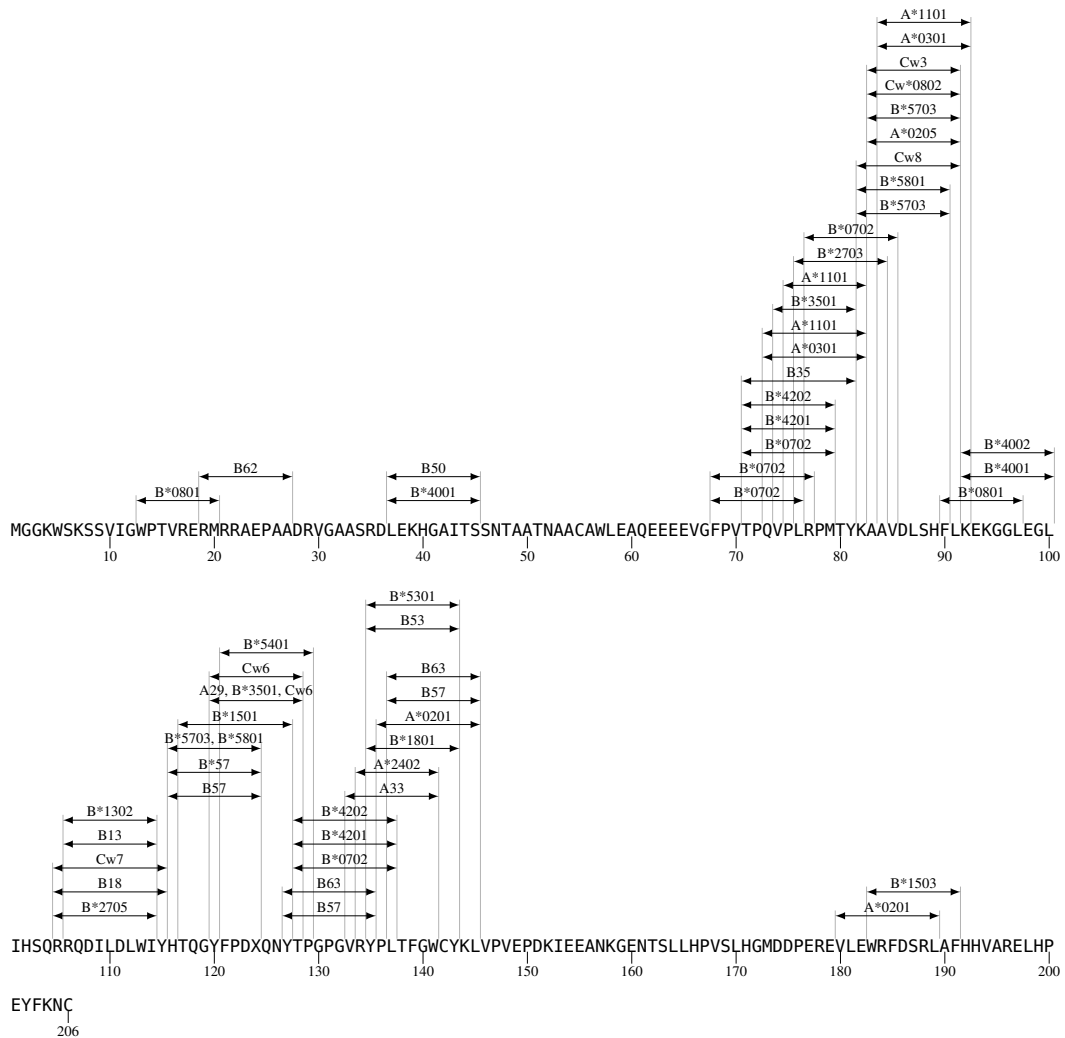
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Optimal HIV-1 CTL Epitopes

Map of optimal HIV-1 CTL epitopes



Nef Optimal CTL Epitope Map



Review

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