I-A

The 2019 Optimal HIV CTL Epitopes Update: Growing Diversity in Epitope Length and HLA Restriction

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I-A-1 Introduction

Over the 20 years since it's first edition, the Los Alamos National Laboratory HIV Immunology database's "Optimal CTL epitope list" has grown from a mere 60 epitopes in 1995 to a collection of close to 350 epitopes for which specific HLA class I restriction and optimal peptide length have been experimentally defined. The collective information, gathered from many laboratories worldwide and oftentimes with generous contributions of unpublished data, has allowed the field to better characterize the T-cell response to HIV infection, to gain important insights into mechanisms of viral evolution and viral adaptation to the host immune surveillance and to critically support different HIV vaccine designs [Mothe *et al.*, 2015; Moyo *et al.*, 2019; Rolland *et al.*, 2007; Gaiha *et al.*, 2019]. It has also helped to refine HLA binding-motifs and facilitated structural and molecular analyses of T cell receptors involved in pathogen-specific immune responses. Over the years, we have tried to adjust inclusion criteria for this listing to the standards and technical advances made in the field, in order to maximize coverage of described epitopes while not negatively impacting the accuracy of information on their HLA restriction and definition of optimal epitope length. However, the extensive degree of HLA binding promiscuity, the potential role of T cells with non-classical HLA restriction and data emerging from epitope elution analyses continuously challenge our guidelines for inclusion. Thus, every update of the "Epitope A-list" has seen more or less extensive modifications, based on newly adopted criteria, new data published, and removal of previously included epitope sequences that were shown to be inaccurate.

The 2019 update adheres to the inclusion criteria which require i) experimental demonstration of HLA class I restriction (through specific presentation on antigen presenting cells expressing the defined HLA allele(s) or by stable tetramer formation and staining in flow cytometry assays) and ii) the definition of the shortest, most potent epitope sequence, ideally defined by using end-point dilutions of serial single-amino acid truncations. Aside from adding almost 40 new epitopes in this update, we have also reviewed the HLA information for epitopes that only had 2-digit HLA class I allele information. In several cases, we have thus been able to identify the actual presenting 4-digit class I allele(s) from the published literature, leading to the inclusion of some epitopes with assigned restrictions to different subtypes of the same 2-digit allele. This has been the case in the past, for alleles such as HLA-A*02, -A*26, -B*27 and –B*44, where different subtypes present the same epitope, and has been extended now to alleles such as HLA-B*14 and others, where detailed studies, additional HLA typing or re-analyses of existing data have shown presentation by one or more of the different 4-digit subtypes [Leitman *et al.*, 2017; Frahm *et al.*, 2006]. The distinction of restricting HLA subtypes is especially important for those alleles where the binding preferences vary between subtypes (most prominently the HLA-B*15 and A68 loci) and/or have been linked to distinctively different HIV disease outcomes (such as HLA-B*35 and B*58). A few, mainly older epitopes, for which allele subtype information was not available remain listed with only a 2-digit HLA restriction, which does not imply that they are presented across different subtypes of the given HLA allele.

Also of relevance for an accurate reflection of targeted T-cell epitopes in HIV and for the definition of optimal epitopes are the emerging data on epitope length variants. While many elution studies have assessed peptides from regular antigen presenting cells expressing all three clas-

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sical HLA-A, -B and –C loci, some laboratories have developed systems where only a single allele is expressed and the peptide-loaded class I molecules are being secreted in the culture supernatant [Weidanz *et al.*, 2007]. This ensures that a) only epitopes from a single allele are being studied and b) epitope processing intermediates, which are generally captured in whole-cell approaches, are unlikely to confound the analyses [Rucevic *et al.*, 2016; Yaciuk *et al.*, 2014]. In one of these studies, epitopes from HLA-A*1101-secreting, HIV infected and uninfected cells were eluted and analyzed [Yaciuk *et al.*, 2014]. While the majority of epitopes eluted were in the expected range of known HLA-A*11 restricted epitopes (9-11mers), there was a substantial number of ligands that were between 12 and 15 amino acids in length, with some eluted sequences being even longer. Importantly, this was the case for both, host protein ligands and HIV-derived peptides, suggesting that HIV infection did not grossly change the processing machinery in regards to the length of peptides produced. In addition, about 90% of the eluted peptides had a C-terminal anchor consisting of Lysine or Arginine, again in line with published motif data for HLA-A*1101 and not significantly different between ligands originating from self or from viral proteins. There was also remarkable consistency in the anchor position at the B-pocket, suggesting that some of the longer epitopes may be presented as bulged ligands [Burrows *et al.*, 2006]. Regardless of the final structural characteristics of the HLA-peptide complex though, it is quite likely that T-cell receptors (TCR) would be available that can recognize structures with very long peptides. Indeed, further immunogenicity analyses in the HLA-A*1101 study above indicated broad in-vitro reactivity of these longer peptides [Yaciuk *et al.*, 2014]. Still, it remains largely unclear whether HIV infection induced distinct T-cell populations with separate specificity for each different epitope length variant or whether the observed responses are due to cross-reactive T-cells recognizing different length variants or embedded epitopes common to the reactive peptides. In the absence of detailed TCR or cross-reactivity analyses, the experimental definition of the "optimal" HLA-A*1101 epitope(s) may be considerably complicated by potential heterogeneous T cells population each recognizing a different epitope length-variant. The use of T cell clones could overcome this issue, but it may prove very labor intensive to isolate and expand clones to different length variants. In addition, the definition of "optimal" epitope length may need to be seen in the context of how responses to the different length variants contribute to virus control *in vivo*. Assessing antigen processing efficacies and binding affinities to the presenting HLA molecules and understanding viral evolution pathways in response to immune pressure exerted on these different length variants may provide a more holistic picture of what the "optimal" length of the presented epitope may be.

For the present listing of epitopes, we have attempted to analyze available data in cases where we identified conflicting reports on epitope length and have used access to overlapping peptide screens and HLA footprint data to best support the final inclusion of a specific epitope. In some cases, sufficient evidence was available to unequivocally call two, partly overlapping or embedded epitopes as distinct entities, each inducing in natural infection its own specific T-cell clonotypes. However, there are generally insufficient data available to discern cross-reactivity from truly separate responses towards partly overlapping or embedded epitopes. Yet, it may be interesting and necessary to identify and clarify these situations since a precise epitope landscape is essential for proper definition of HLA motifs and correct interpretation of HIV CTL escape data. The latter has been subject of a publication [Sun *et al.*, 2014], that has reported multipronged targeting of the same epitope region in the context of one single HLA class I allele. Without detailed knowledge of the precise epitope boundaries, the interpretation of subsequent CTL escape and HLA footprint analyses will be flawed. But the issue goes evidently well beyond just describing epitope sequences for a listing as the present one since the targeting of the same region of the viral protein(s) with partly overlapping CTL specificities may complicate viral immune evasion considerably and mediate superior viral control *in vivo*. Just how extensive this issue is, is highlighted by our own analyses of potential "shifted" epitopes around defined optimal epitopes: by screening just 5 amino acids up- and downstream of each described optimal epitope for suitable anchor positions satisfying the allele-specific binding motif and allowing for an epitope length of 9 to 12 amino acids, the number of potential independent epitopes that could bind the given HLA class I molecule and induce T cell responses to the same region increased by more than 120% [Silva-Arrieta *et al.*, unpublished]. Of course, responses to such shifted epitopes will be measured when using longer test peptides; but further, detailed epitope mapping would be required to discriminate responses to the different epitope length variants overlapping the known optimal epitope.

The presence of shifted epitopes also has potential implications on HIV vaccine design. If it turns out that targeting the same region of the viral proteome by T cells with specificities for partly overlapping or embedded epitopes is critical to avoid viral immune escape, then it would likely be advantageous to induce such responses by using longer epitope sequences rather than just sequences truncated down to the most potent, shortest epitopes, *i.e.* optimal epitope. Hence, vaccine immunogen sequences based on optimal epitope strings may not perform as well as desired since the virus could more readily evade this single T cell specificity. The notion that overlapping epitope responses may drive viral evolution *in vivo* is also supported by the identification of HLA footprints in flanking sequences of optimally defined epitopes. These have only occasionally been attributed to the occurrence of effective antigen processing escape mutations [Draenert *et al.*, 2004c; Brander *et al.*, 1999] and a renewed look at defined HLA footprints close to described optimal epitopes may help to elucidate the impact of multiple T cell specificities on the same epitope region.

In light of recent reports that suggest a potential role for virus-specific T cells with non-classical HLA restriction, we have also considered the inclusion of T cell epitopes presented by HLA-E alleles and other non-classical class I molecules as well as epitopes presented by HLA class II molecules but targeted by CD8+ T cells [Hansen *et al.*, 2013; D'Souza *et al.*, 2019; Hannoun *et al.*, 2018]. We feel that the experimental data on these responses are too preliminary at this time and the relevance to HIV infection too uncertain to warrant wide inclusion in the A-list. We will however keep on monitoring the literature and include epitopes with non-classical restriction as they become fully defined. Another source of "non-classical epitopes" may be those encoded in alternative and antisense reading frames of HIV. The existence of immunogenic epitopes in both settings has repetitively been demonstrated but the epitopes have rarely been defined to the optimal epitope level [Berger *et al.*, 2010; Berger *et al.*, 2015; Bansal *et al.*, 2010; Bansal *et al.*, 2015; Bet *et al.*, 2015]. Although their antiviral effects need to be still determined, frameshifted epitopes may still be expressed, processed and presented in cells that do not contain replication competent virus (as are many other "conventional" epitopes) and contributing to the shaping of the virus-specific T cell response and, in turn, the proviral landscape [Pollack *et al.*, 2017]. Finally, other non-classical epitopes may include those that have been described as HLA-class I binders important for NK cell interaction but which may not necessarily induce a T cell response [Hölzemer *et al.*, 2015; Alter *et al.*, 2011]. While they could be critical for NK activity and NK-mediated elimination of infected cells, they likely escape current screening approaches and one would need to define additional experimental criteria to include them in the A-list.

As always, we are grateful to the numerous laboratories that continue to provide additional information and unpublished data to compile the current update and apologize if we should have overlooked some epitope sequences that merit inclusion. We appreciate any further additional information on new epitopes until the next update, especially also if investigators wish to contribute data on epitope length that may conflict with current entries in this 2019 update.

Review

I-A-2 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 *et al.*, 2006
A*0201 (A2)	p17	77–85	SLYNTVATL	Johnson *et al.*, 1991; Parker *et al.*, 1992; Parker *et al.*, 1994
A*0201 (A2)	p17	77–86	SLFNTVATLY	Tenzer *et al.*, 2009
A*0201 (A2)	p2p7p1p6	70–79	FLGKIWPSYK	Yu *et al.*, 2002b
A*0201 (A2)	Protease	76–84	LVGPTPVNI	Konya *et al.*, 1997
A*0201 (A2)	RT	33–41	ALVEICTEM	Haas *et al.*, 1998; Haas, 1999
A*0201 (A2)	RT	179–187	VIYQYMDDL	Harrer *et al.*, 1996a
A*0201 (A2)	RT	179–189	VIYQYMDDLYV	Borthwick *et al.*, 2017
A*0201 (A2)	RT	309–317	ILKEPVHGV	Walker *et al.*, 1989; Tsomides *et al.*, 1991
A*0201 (A2)	RT	550–559	KLVSQGIRKV	Ahmed *et al.*, 2016; Borthwick *et al.*, 2017
A*0201 (A2)	Vpr	59–67	AIIRILQQL	Altfeld *et al.*, 2001b; Altfeld *et al.*, 2001a
A*0201 (A2)	gp160	311–320	RGPGRAFVTI	Alexander-Miller *et al.*, 1996
A*0201 (A2)	gp160	813–822	SLLNATDIAV	Dupuis *et al.*, 1995
A*0201 (A2)	gp160	814–822	LLNATDIAV	Dupuis *et al.*, 1995; Brander *et al.*, 1995
A*0201 (A2)	Nef	136–145	PLTFGWCYKL	Haas *et al.*, 1996; Maier *et al.*, 1999
A*0201 (A2)	Nef	180–189	VLEWRFDSRL	Haas *et al.*, 1996; Maier *et al.*, 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	RIRQGLERA	Sabbaj *et al.*, 2003
A*0205 (A2)	Nef	83–91	GAFDLSFFL	Rathod, 2006
A*0206	RT	127–135	YTAFTIPSI	Watanabe *et al.*, 2013
A*0207 (A2)	p24	164–172	YVDRFYKTL	Currier *et al.*, 2002

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

HLA	Protein	AA	Sequence	Reference
A*0301 (A3)	p17	18–26	KIRLRPGGK	Harrer *et al.*, 1996b
A*0301 (A3)	p17	20–28	RLRPGGKKK	Goulder *et al.*, 1997d; Culmann, 1999; Lewinsohn *et al.*, 1999; Wilkes *et al.*, 1999a
A*0301 (A3)	p17	20–29	RLRPGGKKKY	Goulder *et al.*, 2000b
A*0301 (A3)	RT	33–43	ALVEICTEMEK	Haas *et al.*, 1998; Haas, 1999
A*0301 (A3)	RT	73–82	KLVDFRELNK	Yu *et al.*, 2002a
A*0301 (A3)	RT	93–101	GIPHPAGLK	Yu *et al.*, 2002a
A*0301 (A3)	RT	158–166	AIFQSSMTK	Threlkeld *et al.*, 1997
A*0301 (A3)	RT	269–277	QIYPGIKVR	Yu *et al.*, 2002a
A*0301 (A3)	RT	356–366	RMRGAHTNDVK	Yu *et al.*, 2002a
A*0301 (A3)	Integrase	179–188	AVFIHNFKRK	Yu *et al.*, 2002a
A*0301 (A3)	Vif	17–26	RIRTWKSLVK	Altfeld *et al.*, 2001b; Yu *et al.*, 2002a
A*0301 (A3)	Vif	28–36	HMYISKKAK	Yu *et al.*, 2002a
A*0301 (A3)	Vif	158–168	KTKPPLPSVKK	Yu *et al.*, 2002a
A*0301 (A3)	Rev	57–66	ERILSTYLGR	Addo, 2002; Yu *et al.*, 2002a
A*0301 (A3)	gp160	37–46	TVYYGVPVWK	Johnson *et al.*, 1994a
A*0301 (A3)	gp160	770–780	RLRDLLLIVTR	Takahashi *et al.*, 1991
A*0301 (A3)	Nef	73–82	QVPLRPMTYK	Koenig *et al.*, 1990; Culmann *et al.*, 1991
A*0301 (A3)	Nef	84–92	AVDLSHFLK	Yu *et al.*, 2002a
A*0301 (A3)	Cryptic		RTSKASLER	Berger *et al.*, 2010 frameshifted Pol 236–244
A11	Integrase	203–211	IIATDIQTK	Wang *et al.*, 2007
A*1101 (A11)	p17	84–91	TLYCVHQK	Harrer *et al.*, 1998
A*1101 (A11)	p24	217–227	ACQGVGGPGHK	Sipsas *et al.*, 1997
A*1101 (A11)	RT	117–126	SVPLDEGFRK	Ahmed *et al.*, 2016
A*1101 (A11)	RT	117–126	SVPLDEGFRK	Borthwick *et al.*, 2017
A*1101 (A11)	RT	156–165	SPAIFQSSMTK	Borthwick *et al.*, 2017
A*1101 (A11)	RT	158–166	AIFQSSMTK	Johnson *et al.*, 1994b; Zhang *et al.*, 1993; Threlkeld *et al.*, 1997
A*1101 (A11)	RT	341–350	IYQEPFKNLK	Culmann, 1999
A*1101 (A11)	RT	520–528	QIIEQLIKK	Fukada *et al.*, 1999
A*1101 (A11)	Integrase	179–188	AVFIHNFKRK	Fukada *et al.*, 1999
A*1101 (A11)	gp160	199–207	SVITQACPK	Fukada *et al.*, 1999
A*1101 (A11)	Nef	73–82	QVPLRPMTYK	Buseyne, 1999
A*1101 (A11)	Nef	75–82	PLRPMTYK	Culmann *et al.*, 1991
A*1101 (A11)	Nef	84–92	AVDLSHFLK	Culmann *et al.*, 1991
A23	gp160	585–593	RYLKDQQLL	Cao *et al.*, 2003
A*2402 (A24)	p17	28–36	KYKLKHIVW	Ikeda-Moore *et al.*, 1998; Lewinsohn, 1999
A*2402 (A24)	p24	162–172	RDYVDRFFKTL	Dorrell *et al.*, 1999; Rowland-Jones, 1999
A*2402 (A24)	gp160	52–61	LFCASDAKAY	Lieberman *et al.*, 1992; Shankar *et al.*, 1996
A*2402 (A24)	gp160	585–593	RYLKDQQLL	Dai *et al.*, 1992
A*2402 (A24)	Nef	126–135	NYTPGPGIRY	Han *et al.*, 2014; Llano *et al.*, 2017
A*2402 (A24)	Nef	134–141	RYPLTFGW	Goulder *et al.*, 1997c; Ikeda-Moore *et al.*, 1998
A*2402 (A24)	Nef	134–143	RYPLTFGWCF	Sun *et al.*, 2014
A*2501 (A25)	p24	13–23	QAISPRTLNAW	Kurane *et al.*, 1999
A*2501 (A25)	p24	71–80	ETINEEAAEW	Klenerman *et al.*, 1996; van Baalen *et al.*, 1996
A*2501 (A25)	gp160	321–330	EIIGDIRQAY	Liu *et al.*, 2006

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

HLA	Protein	AA	Sequence	Reference
A*2601 (A26)	p24	35–43	EVIPMFSAL	Goulder *et al.*, 1996b
A*2601 (A26)	RT	449–457	ETKLGKAGY	Sabbaj *et al.*, 2003
A*2602 (A26)	p24	35–43	EVIPMFSAL	Kawashima *et al.*, 2008
A*2603 (A26)	p24	35–43	EVIPMFSAL	Kawashima *et al.*, 2008
A29	Nef	120–128	YFPDWQNYT	Draenert *et al.*, 2004a
A*2902 (A29)	p17	78–86	LYNTVATLY	Masemola *et al.*, 2004
A*2902 (A29)	gp160	209–217	SFEPIPIHY	Altfeld, 2000
A30	p17	34–44	LVWASRELERF	Masemola *et al.*, 2004
A*3001	Vif	18–26	IRTWKSLVK	Borthwick *et al.*, 2017
A*3002 (A30)	p17	76–86	RSLYNTVATLY	Goulder *et al.*, 2001
A*3002 (A30)	RT	173–181	KQNPDIVIY	Goulder *et al.*, 2001
A*3002 (A30)	RT	263–271	KLNWASQIY	Goulder *et al.*, 2001
A*3002 (A30)	RT	356–365	RMRGAHTNDV	Sabbaj *et al.*, 2003
A*3002 (A30)	Integrase	219–227	KIQNFRVYY	Sabbaj *et al.*, 2003; Rodriguez *et al.*, 2004
A*3002 (A30)	gp160	310–318	HIGPGRAFY	Sabbaj *et al.*, 2003
A*3002 (A30)	gp160	704–712	IVNRNRQGY	Goulder *et al.*, 2001
A*3002 (A30)	gp160	794–802	KYCWNLLQY	Goulder *et al.*, 2001
A*3101 (A31)	gp160	770–780	RLRDLLLIVTR	Safrit *et al.*, 1994a; Safrit *et al.*, 1994b
A*3201 (A32)	RT	392–401	PIQKETWETW	Harrer *et al.*, 1996b
A*3201 (A32)	gp160	419–427	RIKQIINMW	Harrer *et al.*, 1996b
A33	Nef	133–141	TRYPLTFGW	Cao, 2002
A*3303 (A33)	Vpu	29–37	EYRKILRQR	Addo *et al.*, 2002
A*3303 (A33)	gp160	698–707	VFAVLSIVNR	Hossain *et al.*, 2001
A*3303 (A33)	gp160	831–838	EVAQRAYR	Hossain *et al.*, 2001
A66	RT	438–448	ETFYVDGAANR	Rathod, 2006
A*6801 (A68)	Vpr	52–62	DTWAGVEAIIR	Sabbaj *et al.*, 2004
A*6801 (A68)	Tat	39–49	ITKGLGISYGR	Oxenius *et al.*, 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	430–437	ETFYVDGA	Kløverpris *et al.*, 2013b
A*6802 (A68)	RT	436–445	GAETFYVDGA	Rathod *et al.*, 2005
A*6802 (A68)	Vpr	48–57	ETYGDTWTGV	Rathod *et al.*, 2005
A*6802 (A68)	gp160	777–785	IVTRIVELL	Wilkes, 1999
A*7401 (A19)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999

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

HLA	Protein	AA	Sequence	Reference
B7	p24	84–92	HPVHAGPIA	Yu *et al.*, 2002a; Westrop *et al.*, 2009
B7	RT	156–164	SPAIFQSSM	Linde *et al.*, 2006
B7	Rev	66–75	RPAEPVPLQL	Yang, 2006
B*0702 (B7)	p17	22–30	RPGGKKHYM	Kløverpris *et al.*, 2014
B*0702 (B7)	p24	16–24	SPRTLNAWV	Lewinsohn, 1999
B*0702 (B7)	p24	48–56	TPQDLNTML	Wilson, 1999; Wilkes *et al.*, 1999b; Jin *et al.*, 2000; Wilson *et al.*, 1997
B*0702 (B7)	p24	223–231	GPGHKARVL	Goulder, 1999
B*0702 (B7)	p2p7p1p6	44–52	APRKKGCWK	Luo *et al.*, 2012
B*0702 (B7)	RT	156–165	SPAIFQSSMTK	Borthwick *et al.*, 2017
B*0702 (B7)	Vpr	34–42	FPRIWLHGL	Altfeld *et al.*, 2001b
B*0702 (B7)	Vif	48–57	HPRVSSEVHI	Altfeld *et al.*, 2001b
B*0702 (B7)	gp160	298–307	RPNNNTRKSI	Safrit *et al.*, 1994b
B*0702 (B7)	gp160	843–851	IPRRIRQGL	Wilkes *et al.*, 1999a
B*0702 (B7)	Nef	68–77	FPVTPQVPLR	Haas *et al.*, 1996; Maier *et al.*, 1999
B*0702 (B7)	Nef	68–76	FPVTPQVPL	Bauer *et al.*, 1997; Frahm *et al.*, 2002
B*0702 (B7)	Nef	71–79	TPQVPLRPM	Goulder, 1999
B*0702 (B7)	Nef	77–85	RPMTYKAAL	Bauer *et al.*, 1997
B*0702 (B7)	Nef	128–137	TPGPGVRYPL	Culmann-Penciolelli *et al.*, 1994; Haas *et al.*, 1996
B8	gp160	848–856	RQGLERALL	Cao, 2002
B*08 (B8)	Nef	187–195	SRLAFHHMA	Migueles *et al.*, 2015
B*0801 (B8)	p17	24–32	GGKKKYKLK	Reid *et al.*, 1996; Goulder *et al.*, 1997b
B*0801 (B8)	p17	74–82	ELRSLYNTV	Goulder *et al.*, 1997b
B*0801 (B8)	p24	128–135	EIYKRWII	Sutton *et al.*, 1993; Goulder *et al.*, 1997b
B*0801 (B8)	p24	197–205	DCKTILKAL	Sutton *et al.*, 1993
B*0801 (B8)	RT	18–26	GPKVKQWPL	Walker *et al.*, 1989; Sutton *et al.*, 1993
B*0801 (B8)	Integrase	259–268	VVPRRKAKII	Borthwick *et al.*, 2017
B*0801 (B8)	Integrase	263–273	RKAKIIRDYGK	Borthwick *et al.*, 2017
B*0801 (B8)	Integrase	265–273	KIIRDYGK	Borthwick *et al.*, 2017
B*0801 (B8)	gp160	2–10	RVKEKYQHL	Sipsas *et al.*, 1997
B*0801 (B8)	gp160	586–593	YLKDQQLL	Johnson *et al.*, 1992; Shankar *et al.*, 1996
B*0801 (B8)	Nef	13–20	WPTVRERM	Goulder *et al.*, 1997b
B*0801 (B8)	Nef	90–97	FLKEKGGL	Culmann-Penciolelli *et al.*, 1994; Price *et al.*, 1997
B13	p24	3–11	VQNLQGQMV	Honeyborne *et al.*, 2007
B13	p24	94–104	GQMREPRGSDI	Honeyborne *et al.*, 2007
B13	p2p7p1p6	66–74	RQANFLGKI	Honeyborne *et al.*, 2007
B13	Protease	57–66	RQYDQILIEI	Honeyborne *et al.*, 2007; Mueller *et al.*, 2007
B13	RT	333–341	GQGQWTYQI	Honeyborne *et al.*, 2007
B13	Nef	106–114	RQDILDLWI	Harrer *et al.*, 2005; Honeyborne *et al.*, 2007
B*1302 (B13)	p24	8–15	GQMVHQAI	Shahid *et al.*, 2015
B*1302 (B13)	Nef	106–114	RQDILDLWV	Gray *et al.*, 2009
B14	p2p7p1p6	42–50	CRAPRKKGC	Yu *et al.*, 2002b
B*14 (B14)	Nef	83–91	AAVDLSHFL	Migueles *et al.*, 2015

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

HLA	Protein	AA	Sequence	Reference
B*1401 (B14)	RT	142–149	IRYQYNVL	Rathod, 2006
B*1402 (B14)	p24	166–174	DRFYKTLRA	Harrer *et al.*, 1996b
B*1402 (B14)	gp160	584–592	ERYLKDQQL	Johnson *et al.*, 1992
B*1501 (B62)	p24	137–145	GLNKIVRMY	Johnson *et al.*, 1991; Goulder, 1999
B*1501 (B62)	RT	260–271	LVGKLNWASQIY	Johnson, 1999
B*1501 (B62)	RT	309–318	ILKEPVHGVY	Johnson *et al.*, 1991; Johnson, 1999
B*1501 (B62)	Nef	117–127	TQGYFPDWQNY	Culmann, 1999
B*1503 (B72)	p24	24–32	VKVIEEKAF	Honeyborne *et al.*, 2005
B*1503 (B72)	p24	164–172	YVDRFFKTL	Masemola *et al.*, 2004
B*1503 (B72)	Protease	68–76	GKKAIGTVL	Rathod *et al.*, 2006b
B*1503 (B72)	RT	496–505	VTDSQYALGI	Sabbaj *et al.*, 2003
B*1503 (B72)	Integrase	135–143	IQQEFGIPY	Honeyborne *et al.*, 2005
B*1503 (B72)	Integrase	185–194	FKRKGGIGGY	Honeyborne, 2003
B*1503 (B72)	Integrase	263–271	RKAKIIRDY	Cao *et al.*, 2003
B*1503 (B72)	Tat	38–47	FQTKGLGISY	Novitsky *et al.*, 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 *et al.*, 2007
B*1510 (B71)	Vif	79–87	WHLGHGVSI	Honeyborne, 2003
B*1516 (B63)	gp160	375–383	SFNCGGEFF	Wilson *et al.*, 1997; Wilson, 1999
B18	RT	137–146	NETPGIRYQY	Rathod *et al.*, 2006b
B18	RT	175–183	NPEIVIYQY	Rathod, 2006
B18	Nef	105–115	RRQDILDLWVY	Yang, 2006
B*1801 (B18)	p24	161–170	FRDYVDRFYK	Ogg *et al.*, 1998
B*1801 (B18)	RT	174–184	EIVIYQYMD	Borthwick *et al.*, 2017
B*1801 (B18)	Vif	87–94	IEWRLRRY	Kloverpris *et al.*, 2017
B*1801 (B18)	Vif	102–111	LADQLIHLHY	Altfeld *et al.*, 2001b
B*1801 (B18)	gp160	31–39	AENLWVTVY	Liu *et al.*, 2006
B*1801 (B18)	gp160	61–69	YETEVHNVW	Liu *et al.*, 2006
B*1801 (B18)	Nef	135–143	YPLTFGWCY	Culmann *et al.*, 1991; Culmann-Penciolelli *et al.*, 1994
B27	Vpr	31–39	VRHFPRIWL	Addo *et al.*, 2004
B*2703 (B27)	p24	131–140	RRWIQLGLQK	Rowland-Jones *et al.*, 1998; Rowland-Jones, 1999
B*2703 (B27)	Nef	76–84	LRPMTYKAA	Huang *et al.*, 2010
B*2705 (B27)	p17	19–27	IRLRPGGKK	McKinney *et al.*, 1999; Lewinsohn, 1999
B*2705 (B27)	p24	131–140	KRWIILGLNK	Nixon *et al.*, 1988; Buseyne *et al.*, 1993; Goulder *et al.*, 1997a
B*2705 (B27)	Integrase	186–194	KRKGGIGGY	Payne *et al.*, 2009
B*2705 (B27)	Vif	18–27	IRTWKSLVKH	Borthwick *et al.*, 2017
B*2705 (B27)	gp160	786–795	GRRGWEALKY	Lieberman *et al.*, 1992; Lieberman, 1999
B*2705 (B27)	Nef	105–114	RRQDILDLWI	Goulder *et al.*, 1997d

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

HLA	Protein	AA	Sequence	Reference
B35	Nef	71–81	RPQVPLRPMTY	Motozono *et al.*, 2009
B*3501 (B35)	p17	36–44	WASRELERF	Goulder *et al.*, 1997c
B*3501 (B35)	p17	124–132	NSSKVSQNY	Rowland-Jones *et al.*, 1995
B*3501 (B35)	p24	84–92	HPVHAGPIA	Westrop *et al.*, 2009; Matthews *et al.*, 2012
B*3501 (B35)	p24	121–130	NPPIPVGDIY	Matthews *et al.*, 2012
B*3501 (B35)	p24	122–130	PPIPVGDIY	Rowland-Jones *et al.*, 1995
B*3501 (B35)	RT	107–115	TVLDVGDAY	Wilkes *et al.*, 1999a; Wilson *et al.*, 1999
B*3501 (B35)	RT	118–127	VPLDEDFRKY	Sipsas *et al.*, 1997; Shiga *et al.*, 1996
B*3501 (B35)	RT	175–183	HPDIVIYQY	Rowland-Jones *et al.*, 1995; Shiga *et al.*, 1996; Sipsas *et al.*, 1997
B*3501 (B35)	RT	293–301	IPLTEEAEL	Tomiyama *et al.*, 2000
B*3501 (B35)	gp160	42–52	VPVWKEATTTL	Wilkes *et al.*, 1999a
B*3501 (B35)	gp160	78–86	DPNPQEVVL	Shiga *et al.*, 1996
B*3501 (B35)	gp160	606–614	TAVPWNASW	Johnson *et al.*, 1994a
B*3501 (B35)	Nef	74–81	VPLRPMTY	Culmann *et al.*, 1991; Culmann-Penciolelli *et al.*, 1994
B*3501 (B35)	Nef	120–128	YFPDWQNYT	Frahm *et al.*, 2007
B*3701 (B37)	Nef	120–128	YFPDWQNYT	Culmann *et al.*, 1991; Culmann, 1999
B*38 (B38)	Pol	227–235	YRDSRDPLW	Migueles *et al.*, 2015
B*3801 (B38)	Vif	79–87	WHLGQGVSI	Sabbaj *et al.*, 2004
B*3801 (B38)	gp160	104–112	MHEDIISLW	Cao, 2002
B*3901 (B39)	p24	61–69	GHQAAMQML	Kurane *et al.*, 1999
B*3910 (B39)	p24	48–56	TPQDLNTML	Honeyborne *et al.*, 2005
B*40	p17	14–24	DRWEKIRLRPG	Migueles *et al.*, 2015
B*40	p17	51–60	LETSEGCRQI	Migueles *et al.*, 2015
B*4001 (B60)	p17	92–101	IEIKDTKEAL	Altfeld *et al.*, 2000
B*4001 (B60)	p24	44–52	SEGATPQDL	Altfeld *et al.*, 2000
B*4001 (B60)	p2p7p1p6	118–126	KELYPLTSL	Yu *et al.*, 2002b
B*4001 (B60)	RT	5–12	IETVPVKL	Draenert *et al.*, 2004b
B*4001 (B60)	RT	202–210	IEELRQHLL	Altfeld *et al.*, 2000
B*4001 (B60)	gp160	805–814	QELKNSAVSL	Altfeld *et al.*, 2000
B*4001 (B60)	Nef	37–45	LEKHGAITS	Draenert *et al.*, 2004b
B*4001 (B60)	Nef	92–100	KEKGGLEGL	Altfeld *et al.*, 2000
B*4002 (B61)	p17	11–19	GELDRWEKI	Sabbaj *et al.*, 2003
B*4002 (B61)	p24	70–78	KETINEEAA	Sabbaj *et al.*, 2003
B*4002 (B61)	p24	78–86	AEWDRVHPV	Sabbaj *et al.*, 2003
B*4002 (B61)	p2p7p1p6	64–71	TERQANFL	Sabbaj *et al.*, 2003
B*4002 (B61)	Integrase	84–93	IEAEVIPAET	Watanabe *et al.*, 2011
B*4002 (B61)	Integrase	197–204	GERIVDII	Watanabe *et al.*, 2011
B*4002 (B61)	Nef	92–100	KEKGGLEGL	Sabbaj *et al.*, 2003; Altfeld *et al.*, 2000
B42	Integrase	260–268	VPRRKAKII	Kiepiela *et al.*, 2002

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

HLA	Protein	AA	Sequence	Reference
B*4201 (B42)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a
B*4201 (B42)	RT	271–279	YPGIKVRQL	Wilkes *et al.*, 1999a
B*4201 (B42)	Integrase	28–36	LPPIVAKEI	Kiepiela *et al.*, 2007
B*4201 (B42)	Integrase	267–275	IIKDYGKQM	Kløverpris *et al.*, 2015
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 *et al.*, 2012
B*4202 (B42)	Nef	128–137	TPGPGVRYPL	Kloverpris *et al.*, 2012
B44	Protease	34–42	EEMNLPGRW	Rodriguez *et al.*, 2004
B44	gp160	31–39	AENLWVTVY	Borrow *et al.*, 1997
B*4402 (B44)	p24	162–172	RDYVDRFYKTL	Ogg *et al.*, 1998
B*4402 (B44)	p24	174–184	AEQASQDVKNW	Lewinsohn, 1999
B*4402 (B44)	gp160	31–40	AENLWVTVYY	Borrow *et al.*, 1997
B*4402/4403	Rev	10–18	EELLKTVRL	Allard *et al.*, 2012
B*4402/4403	Nef	107–115	QEILDLWVY	Karlsson *et al.*, 2012; Adland *et al.*, 2013
B*4403 (B44)	p17	78–86	LYNTVATLY	Masemola *et al.*, 2004
B*4403 (B44)	Nef	93–102	KEKGGLEGLIY	Adland *et al.*, 2013
B*4415 (B12)	p24	28–36	EEKAFSPEV	Bird *et al.*, 2002
B*4501 (B45)	p2p7p1p6	1–10	AEAMSQVTNS	Sabbaj *et al.*, 2004
B*4801 (B48)	p24	181–189	VKNWMTETL	Murakoshi *et al.*, 2009
B*4801 (B48)	p2p7p1p6	66–74	RQANFLGKI	Murakoshi *et al.*, 2009
B50	Nef	37–45	LEKHGAITS	Draenert *et al.*, 2004b
B51	Vif	57–66	IPLGDAKLII	Bansal *et al.*, 2004
B51	Vpr	29–37	EAVRHFPRI	Cao *et al.*, 2003
B*5101 (B51)	p17	22–31	RPGGKKKYKL	Huang *et al.*, 2010
B*5101 (B51)	RT	128–135	TAFTIPSI	Sipsas *et al.*, 1997
B*5101 (B51)	RT	293–301	IPLTEEAEL	Tomiyama *et al.*, 2000
B*5101 (B51)	gp160	416–424	LPCRIKQII	Tomiyama *et al.*, 1999
B*5201 (B52)	p24	143–150	RMYSPTSI	Wilkes *et al.*, 1999a; Wilson *et al.*, 1997
B*5201 (B52)	Integrase	213–220	LQKQITKI	Murakoshi *et al.*, 2017
B53	p24	48–56	TPQDLNMML	Dorrell *et al.*, 2001
B53	Nef	135–143	YPLTFGWCF	Kiepiela *et al.*, 2002
B*5301 (B53)	p24	48–56	TPYDINQML	Gotch *et al.*, 1993
B*5301 (B53)	p24	176–184	QASQEVKNW	Buseyne *et al.*, 1996; Buseyne *et al.*, 1997; Buseyne, 1999
B*5301 (B53)	Nef	135–143	YPLTFGWCY	Sabbaj *et al.*, 2003

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

HLA	Protein	AA	Sequence	Reference
B*5401 (B54)	Protease-RT	99–8	FPISPIETV	Kitano *et al.*, 2008
B*5401 (B54)	RT	149–158	LPQGWKGSPA	Kitano *et al.*, 2008
B*5401 (B54)	Integrase	78–86	HVASGYIEA	Kitano *et al.*, 2008
B*5401 (B54)	Nef	121–129	FPDWQNYTP	Kitano *et al.*, 2008
B*5501 (B55)	gp160	42–51	VPVWKEATTT	Shankar *et al.*, 1996; Lieberman, 1999
B57	p24	32–40	FSPEVIPMF	Frahm *et al.*, 2005
B57	Protease	70–77	KAIGTVLV	Frahm *et al.*, 2005
B57	Integrase	123–132	STTVKAACWW	Rodriguez *et al.*, 2004; Addo *et al.*, 2004
B57	Nef	116–124	HTQGYFPDW	Draenert, 2002
B57	Nef	127–135	YTPGPGIRY	Frahm *et al.*, 2005
B57	Nef	137–145	LTFGWCFKL	Frahm *et al.*, 2005
B*5701 (B57)	p24	15–23	ISPRTLNAW	Johnson *et al.*, 1991; Goulder *et al.*, 1996a
B*5701 (B57)	p24	30–40	KAFSPEVIPMF	Goulder *et al.*, 1996a
B*5701 (B57)	p24	108–117	TSTLQEQIGW	Goulder *et al.*, 1996a
B*5701 (B57)	p24	176–184	QASQEVKNW	Goulder *et al.*, 1996a
B*5701 (B57)	RT	244–252	IVLPEKDSW	van der Burg *et al.*, 1997; Hay, 1999
B*5701 (B57)	Integrase	173–181	KTAVQMAVF	Goulder *et al.*, 1996a; Hay, 1999
B*5701 (B57)	Vif	31–39	ISKKAKGWF	Altfeld *et al.*, 2001b
B*5701 (B57)	Vpr	30–38	AVRHFPRIW	Altfeld *et al.*, 2001b
B*5701 (B57)	Rev	14–23	KAVRLIKFLY	Addo *et al.*, 2001
B*5703 (B57)	p24	30–37	KAFSPEVI	Goulder *et al.*, 2000b
B*5703 (B57)	p24	30–40	KAFSPEVIPMF	Goulder *et al.*, 2000b
B*5703 (B57)	Vif	81–89	LGHGVSIEW	Kløverpris *et al.*, 2013a
B*5703 (B57)	Rev	14–23	QAVRIIKILY	Kløverpris *et al.*, 2013a
B*5703 (B57)	Nef	82–90	KAAFDLSFF	Leslie *et al.*, 2005; Kloverpris *et al.*, 2012
B*5703 (B57)	Nef	83–91	AAFDLSFFL	Gray *et al.*, 2009
B*5703 (B57)	Nef	116–124	HTQGYFPDW	Kløverpris *et al.*, 2013a
B58	p17	76–86	RSLYNTVATLY	Frahm *et al.*, 2005
B58	gp160	59–69	KAYETEVHNVW	Rathod *et al.*, 2006b
B*58 (B58)	Nef	83–91	AAVDLSHFL	Migueles *et al.*, 2015
B*58 (B58)	Nef	119–127	GYFPDWQNY	Migueles *et al.*, 2015
B*5801 (B58)	p24	108–117	TSTLQEQIGW	Goulder *et al.*, 1996a; Bertoletti *et al.*, 1998
B*5801 (B58)	p24	176–184	QASQEVKNW	Gillespie *et al.*, 2005; Kløverpris *et al.*, 2013a
B*5801 (B58)	RT	375–383	IAMESIVIW	Kiepiela *et al.*, 2002
B*5801 (B58)	Rev	14–23	KAVRLIKFLY	Addo *et al.*, 2001
B*5801 (B58)	Nef	82–90	KAAFDLSFF	Leslie *et al.*, 2005
B*5801 (B58)	Nef	116–124	HTQGYFPDW	Kløverpris *et al.*, 2013a
B*5802 (B58)	gp160	577–587	QTRVLAIERYL	Ngumbela *et al.*, 2008
B62	p24	137–145	GLNKIVRMY	Goulder *et al.*, 2000b
B62	Nef	19–27	RMRRAEPAA	Cao, 2002

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

HLA	Protein	AA	Sequence	Reference
B63	p17	76–86	RSLYNTVATLY	Frahm *et al.*, 2005
B63	p24	15–23	ISPRTLNAW	Frahm *et al.*, 2005
B63	p24	30–40	KAFSPEVIPMF	Frahm *et al.*, 2005
B63	Rev	14–23	KAVRLIKFLY	Frahm *et al.*, 2005
B63	Nef	127–135	YTPGPGIRY	Frahm *et al.*, 2005
B63	Nef	137–145	LTFGWCFKL	Frahm *et al.*, 2005
B*73	RT	142–150	IRYQYNVLP	Migueles *et al.*, 2015
B81	Protease	80–90	TPVNIIGRNML	Honeyborne *et al.*, 2006
B81	RT-Integrase	560–8	LFLDGIDKA	Addo, 2002
B*8101 (B81)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a
B*8101 (B81)	Vpr	34–42	FPRIWLHGL	Altfeld *et al.*, 2001b
Cw1	gp160	218–226	CAPAGFAIL	Zuñiga, 2008; Streeck *et al.*, 2008
Cw*0102 (Cw1)	p24	36–43	VIPMFSAL	Goulder *et al.*, 1997c
Cw*0102 (Cw1)	p24	145–153	YSPVSILDI	Buranapraditkun *et al.*, 2011
Cw*0102 (Cw1)	Gag-Pol TF	24–31	NSPTRREL	Liu *et al.*, 2006
Cw*2	Nef	119–127	GYFPDWQNY	Migueles *et al.*, 2015
Cw3	Nef	83–91	AALDLSHFL	Draenert *et al.*, 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 *et al.*, 2002; Trocha, 2002
Cw*0401 (Cw4)	gp160	375–383	SFNCGGEFF	Wilson *et al.*, 1997; Johnson *et al.*, 1993
Cw5	p24	174–185	AEQASQEVKNWM	Draenert *et al.*, 2004b
Cw5	Integrase	114–121	HTDNGSNF	Brockman *et al.*, 2012
C*5	Integrase	114–122	HTDNGSNFT	Migueles *et al.*, 2015
Cw*0501	Rev	67–75	SAEPVPLQL	Addo *et al.*, 2001
Cw6	Nef	120–128	YFPDWQNYT	Frahm *et al.*, 2007
Cw7	Nef	105–115	KRQEILDLWVY	Kiepiela *et al.*, 2002; Yu *et al.*, 2002a
C*07	Nef	134–143	RYPLTFGWCY	Stoll *et al.*, 2015
Cw8	gp160	557–565	RAIEAQQHM	Bishop *et al.*, 2006
Cw8	Nef	82–91	KAAVDLSHFL	Harrer *et al.*, 1996b
Cw*08 (Cw8)	RT	496–503	VTDSQYAL	Migueles *et al.*, 2015
Cw*0802 (Cw8)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a; Honeyborne *et al.*, 2005
Cw*0802 (Cw8)	RT	495–503	IVTDSQYAL	Rathod *et al.*, 2006a
Cw*0802 (Cw8)	Nef	83–91	AAVDLSHFL	Cao *et al.*, 2003; Rathod *et al.*, 2006a

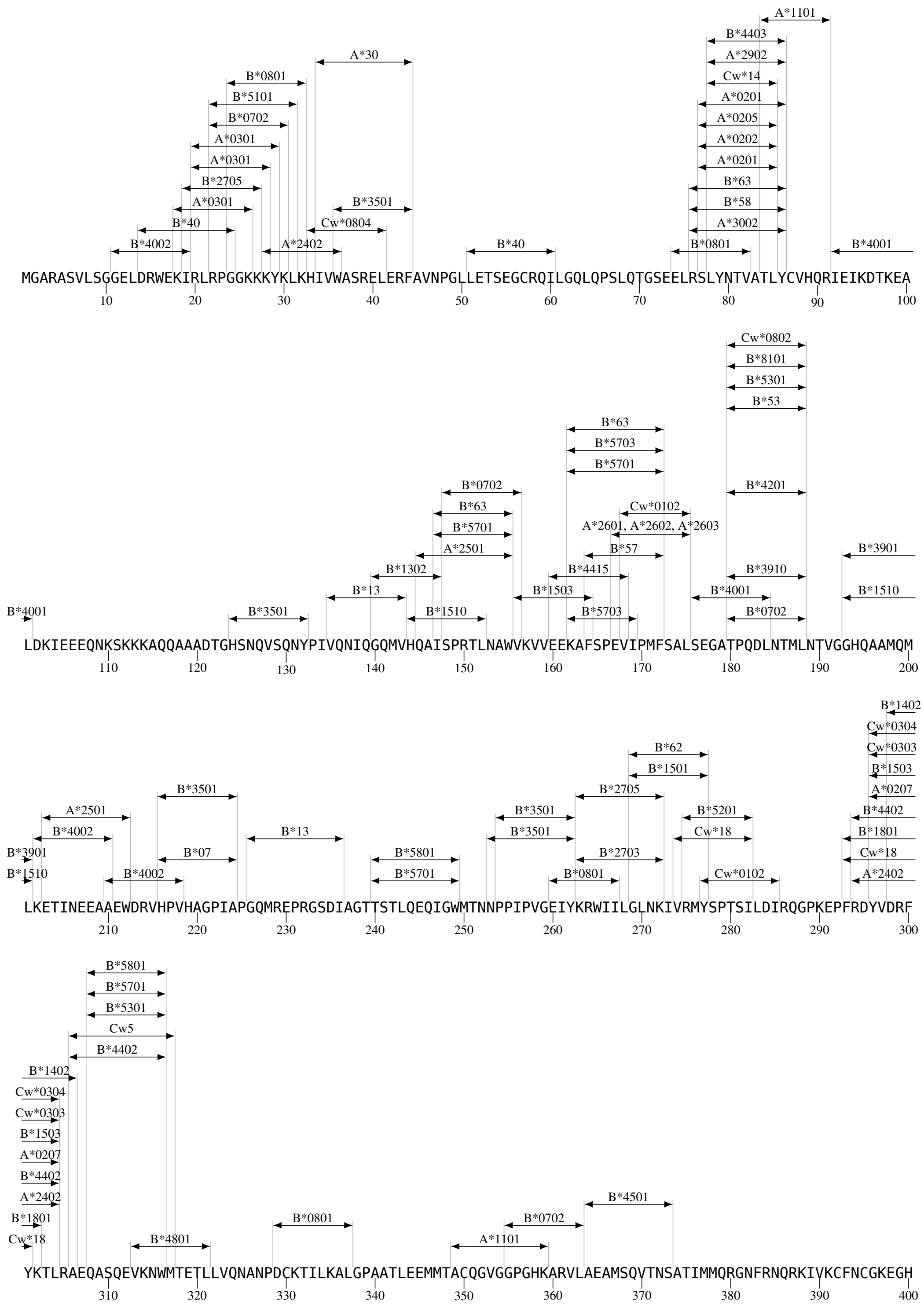
Table I-A-1: Best defined HIV CTL epitopes (cont.).

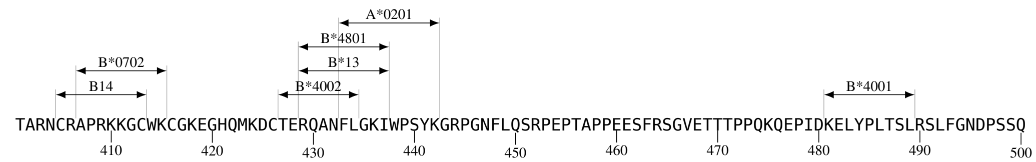
HLA	Protein	AA	Sequence	Reference
Cw*0804 (Cw8)	p17	33–41	HLVWASREL	Masemola *et al.*, 2004
Cw12	Tat	30–37	CCFHCQVC	Cao *et al.*, 2003; Nixon *et al.*, 1999
Cw*1202 (Cw12)	RT	173–181	KQNPDIVIY	Honda *et al.*, 2011
Cw*1202 (Cw12)	RT	309–318	ILKEPVHGVY	Honda *et al.*, 2011
Cw14	p17	78–85	LYNTVATL	Horton *et al.*, 2005
Cw15	gp160	557–565	RAIEAQQHL	Trocha, 2002
Cw18	p24	142–150	VRMYSPVSI	Honeyborne, 2006
Cw18	p24	161–169	FRDYVDRFF	Honeyborne *et al.*, 2005
Cw18	Integrase	165–172	VRDQAEHL	Rathod *et al.*, 2006a
Cw18	Vpu	5–13	YRLGVGALI	Honeyborne, 2006

I-A-3 Map of optimal HIV-1 CTL epitopes

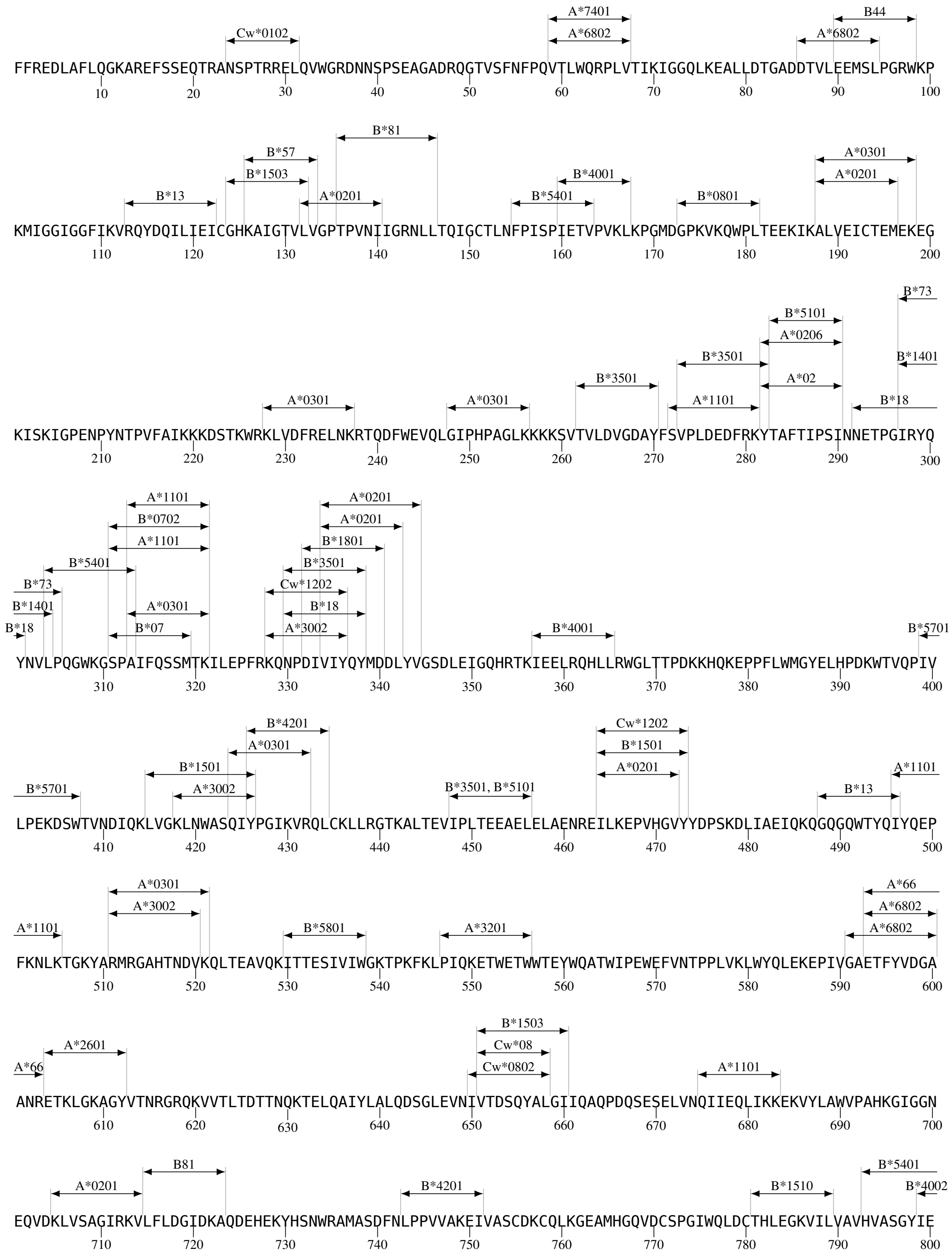
The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence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

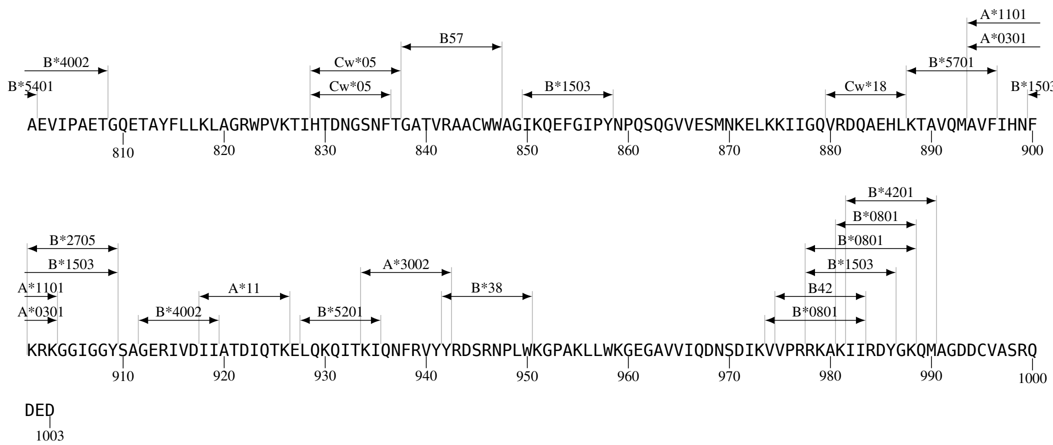
Gag Optimal CTL Epitope Map



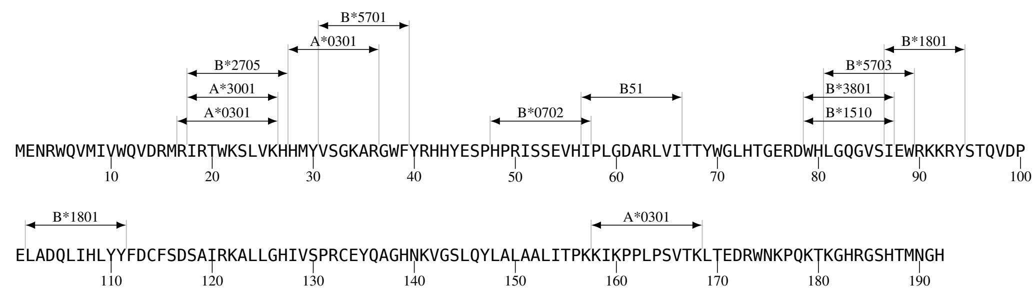


Pol Optimal CTL Epitope Map

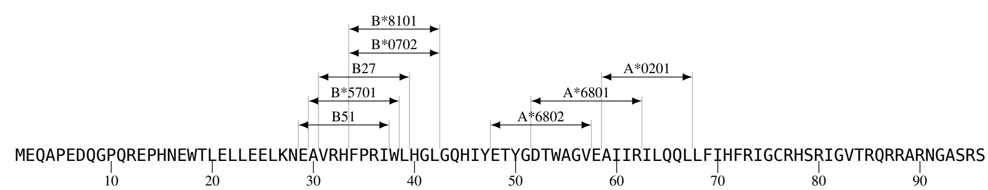




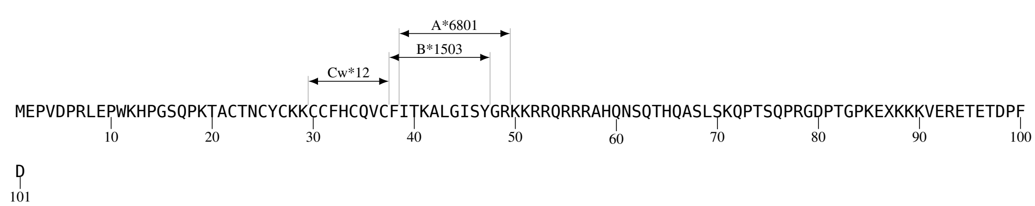
Vif Optimal CTL Epitope Map



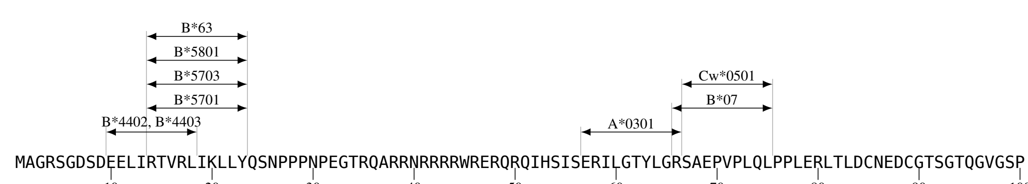
Vpr Optimal CTL Epitope Map



Tat Optimal CTL Epitope Map

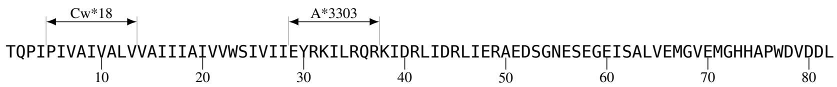


Rev Optimal CTL Epitope Map

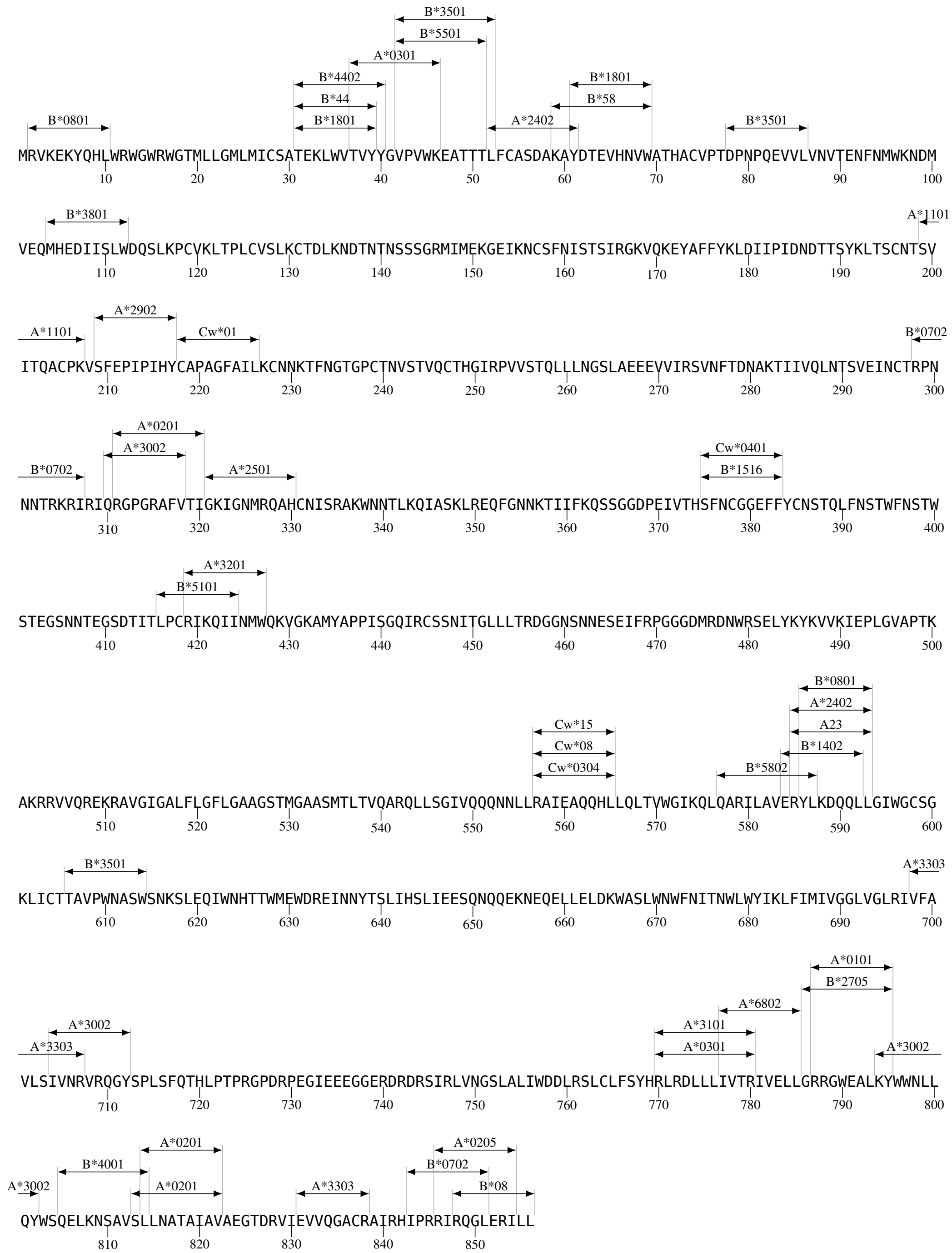


QILVESPTVLESGTKE
110

Vpu Optimal CTL Epitope Map



gp160 Optimal CTL Epitope Map



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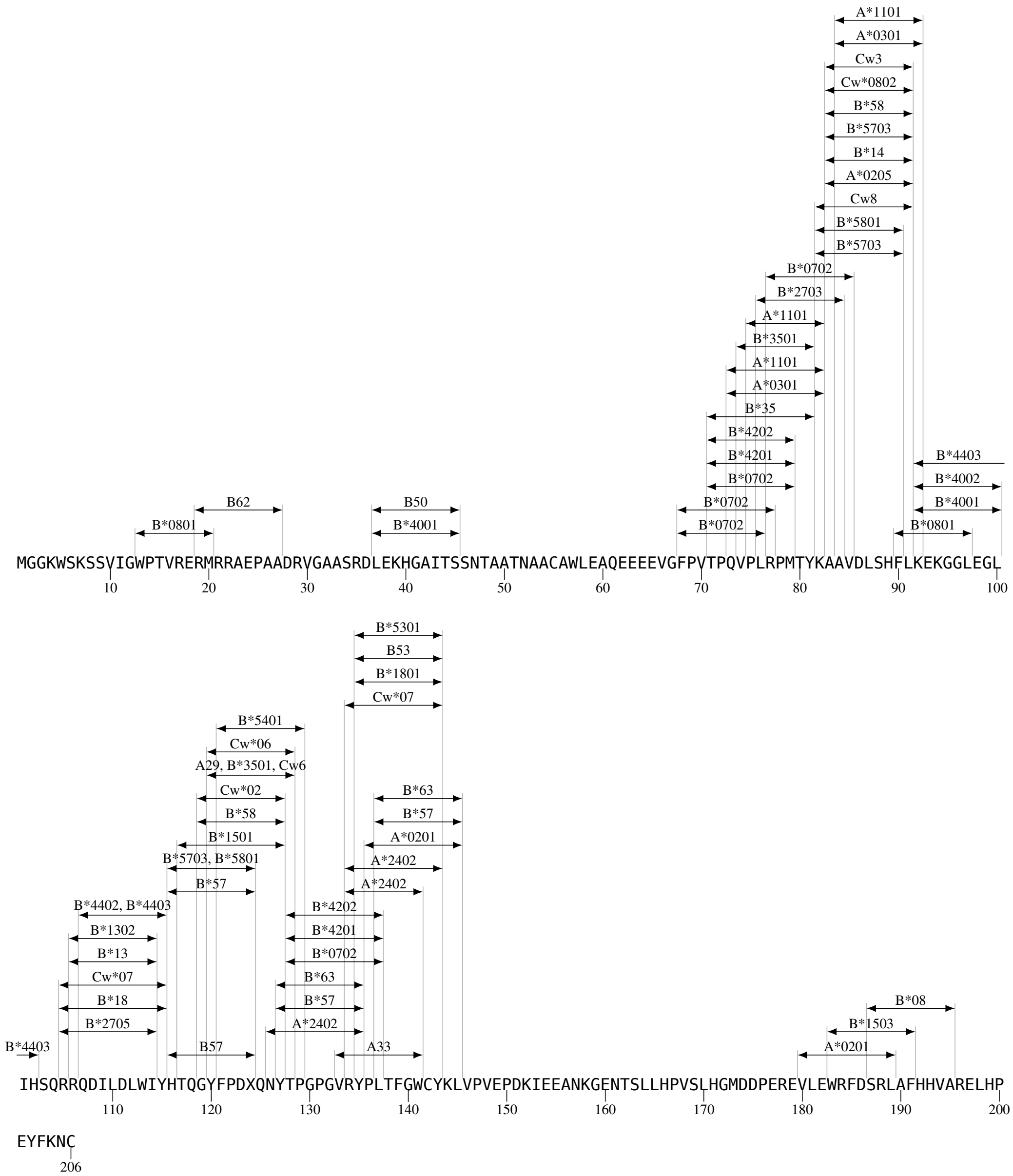
Nef Optimal CTL Epitope Map



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