I-A

How to Optimally Define Optimal Cytotoxic T Lymphocyte Epitopes in HIV Infection?

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I-A-1 The evolution of the optimal CTL epitope list at Los Alamos HIV Immunology database

T-cell responses to HIV infection were first described in 1987, when Walker *et al.* [1987] and Plata *et al.* [1987] independently showed CD8 T-cell reactivity against viral proteins. Soon after, the first epitopes were identified using short synthetic peptides, allowing for ever-increasingly detailed assessments of HIV-specific immune responses and HIV evolution analyses [Kawashima *et al.*, 2009; Nixon *et al.*, 1988]. To date, more than 1200 individual HLA class I-restricted HIV-1 epitopes have been identified, with 276 of these characterized in detail and defined to their minimal or optimal length. With the initiation of large international cohorts of individuals who are in very early stages of infection or who have superior ability to control viral replication, the establishment of multi-national research consortia, and the development of sophisticated viral genome sequencing and analysis tools, many epitopes have been assessed for their relative contribution to the natural control of HIV infection and potential suitability as vaccine immunogens. While many studies take advantage of the detailed description of previously identified and oftentimes immunodominant epitopes, a number of recent studies highlight the importance of subdominant responses, T-cell activities to variable targets, and responses present at the very earliest time points after infection, as these factors may play a crucial role in viral control [Bansal *et al.*, 2005; Frahm *et al.*, 2006; Goonetilleke *et al.*, 2009]. By nature, these responses have not been identified frequently, and in some cases have not undergone the extensive work-up that has been given to the immunodominant responses restricted by frequent HLA class I alleles. The description of such responses poses a challenge to those who strive to provide the HIV community and T-cell immunologist with a reliable resource of well-defined T-cell epitopes. In our attempt to maintain such a resource at the Los Alamos National Laboratory HIV database, we face this challenge frequently, and the following sections outline some of the considerations that shape our product of the "optimal" CTL epitope list.

This year's update of the Los Alamos HIV Immunology Database CTL epitope listing marks the 15th year since we initiated this online list, which has proven a useful tool for the HIV community at large. Based on a few in-house criteria, we have over the years created what we refer to as the "A-list", which contains only those epitopes for which we are fairly confident that they have been defined to their optimal length and for which restriction by a specific HLA class I allele has been indisputably demonstrated. At the same time, we have included in the general section of the database a "B-list" of all T-cell epitopes that have been described in the literature. Thus, within the Los Alamos HIV Immunology database, all studies describing specific T-cell responses to either short peptides or longer segments are included. In addition, search tools on the web site allow rapid searches for these T-cell targets and the retrieval of summarized details about the study in which these responses were defined. As a consequence, any reported T-cell response to HIV should be accessible at LANL, whether it was identified in natural infection or vaccination, including responses defined in individuals with or without specifically defined HLA alleles and with or without a known level of disease control. This information is retained with the epitopes in the full "B-list" database, which can be accessed using a web-based search interface (`http://www.hiv.lanl.gov/content/immunology/ctl_search`). We highlight this fact to encourage anyone accessing the database to go beyond the epitopes given in the A-list whenever the specific study warrants inclusion of less well-defined CTL activities. Including a broader range of epitopes may help to ascertain one's own findings, and potentially allow one to infer, for instance, a potential HLA restriction in a given subject for whom only limited samples are available

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and who thus needs to be analyzed in a less full-blown approach.

I-A-2 Why should we bother with a list of optimally defined epitopes?

As mentioned above, the "optimal/A-list" of HIV epitopes is based on a number of in-house, arbitrary criteria, which we have regularly reviewed over the years. In brief, these criteria include the unequivocal experimental demonstration of restriction by a specific HLA class I allele and the definition of the optimal epitope length. The latter is defined as the peptide truncation that, in its shortest version, elicits a maximal functional response. While in earlier years, serial truncations were often used at decreasing concentrations in cytotoxicity (Cr51 release) assays, more recent studies often use the EliSpot or flow-cytometry based detection of effector functions including cytokine release or expression of CD107. Although these different effector functions have been shown to be subject to variable activation (i.e., peptide concentration) thresholds [Betts *et al.*, 2004], we have not seen or heard of an example in which one or the other marker would have identified different optimal epitope lengths. Aside from HLA restriction and optimal epitope definition, there are no other criteria that we consider for inclusion in the A-list. This practice has sometimes appeared to be overly strict, and a reasonable case can be made for diverging views. While we regularly discuss the input we receive from investigators in the field, our consensus remains to base our selection on the above criteria and to include only the very best defined epitopes in this listing. The major rationale for this is to keep the list free of epitopes that have been defined based on incomplete HLA restriction assays, (mis)interpretation of the data, insufficient arrays of peptide truncations tested or, in a few cases, pure speculation regarding epitope length and HLA restriction. The B list includes essentially all of the epitopes as defined in the published literature by primary authors, thus these less well-defined epitopes are captured in the database as well.

As our optimal epitope list has served as a training set for several epitope prediction algorithms (`http://www.syfpeithi.de/`, `http://atom.research.microsoft.com/bio/epipred.aspx`), we also feel that epitopes that are characterized based on HLA prediction tools should not be included in the A-list. Otherwise, the risk exists that an algorithm may use a training set that contains data that are the product of its own predictions. While this may not be a big issue for those alleles for which many epitopes have been described, cases such as epitopes presented on HLA-B63 (B*1516, B*1517) indicate that existing tools would not have been able to identify the true breath of the allele-specific binding motifs and would have in some cases led to the wrong prediction of optimal epitope length [Frahm *et al.*, 2005]. The prediction of possible HLA restriction is also complicated by the fact that most HIV epitopes can be presented in the context of several different HLA class I alleles [Frahm *et al.*, 2007]. Thus, while the individual response in a single subject will likely provide reliable data, the issue of incorrect, or at least incomplete HLA restriction assignment becomes a real problem in individuals expressing multiple alleles that can present the epitope under study. Apart from the well-described epitope sharing between alleles in the same locus and HLA supertype, such as A3/A11 or B57/B58, individuals mounting, for instance, a response to the known HLA-B37 and B57 `YFPDWQNYT` epitope in Nef, could mount these responses through HLA-A29, -B35, or -C06 [Frahm *et al.*, 2007]. If two or more of these alleles are expressed in a given individual, only a detailed functional HLA restriction analysis could provide reliable HLA restriction information. While this example may seem far-fetched, it only highlights one situation where experimental proof for presentation in the context of at least five alleles has been published. Similar examples exist for HCV epitopes and, in cases where alternatively presenting alleles are encoded by more or less frequent haplotype combinations, will certainly distort immunodominance analyses and have an impact on viral evolution analyses [Niu *et al.*, 2009]). In addition, it is also possible that individuals make responses to a single epitope on more than one of their alleles. This has been analyzed only for a few epitopes and mainly in the context of well-described allele pairs in the same supertype; thus the consequences of a potential "functional homozygosity" (i.e., presentation of a limited set of epitopes on several HLA alleles with similar epitope binding motifs) on viral control *in vivo* and immune evasion of the virus is unknown. Finally, it is also important not to rely on "defining" individual 4-digit typing by inference from larger HLA data sets from unrelated populations and ethnicities. Although haplotype frequencies for well-studied populations have been fairly well established, the ongoing expansion of HIV-related studies and vaccine trials into populations for which these data are limited, introduces a considerable risk of predicting incorrect subtypes. While this may be a particular issue for HLA-B15 and A68 alleles (for which subtypes fall into separate HLA supertypes and thus present vastly different epitopes), the case of HLA-B35 and others (A2, B44, etc.) clearly illustrates that high-resolution typing should be employed for the best definition of HLA restriction [Sidney *et al.*, 2008].

Similar to detailed HLA restriction analyses, there are several reasons why definition of optimal epitope length should be based on experimental analysis rather than binding motif predictions or only partial truncations. While some hints from available epitope sequences may be helpful in the experimental design

of truncation studies or overlapping peptide synthesis (such as the elimination of possible rare ("forbidden") C-terminal residues; `http://www.hiv.lanl.gov/content/sequence/PEPTGEN/peptgen.html`), only a systematic approach will clarify the identity of the targeted sequence. An older example of how this may affect epitope response patterns is the case of two embedded B57 epitopes, where one shorter version is fully contained in a longer epitope sequence [Goulder *et al.*, 2000c]. As shown in our own analyses on promiscuous epitope presentation, embedded epitopes can also be presented on different HLA molecules, again highlighting that HLA restriction and fine mapping approaches need to go hand in hand [Frahm *et al.*, 2007]. Importantly, shorter is not necessarily better, as has been shown in a number of cases where bulged epitopes were presented in the context of alleles such as HLA-B35 and its subtypes [Burrows *et al.*, 2006]. Existing prediction algorithms, trained on existing data of mostly 9–10mer epitope sequences, could not possibly predict these epitopes and their HLA restrictions. Rather, the mapping analyses ideally start from the full-length peptide that initially elicited the detected response (often an overlapping peptide of 15-18 amino acids in length). The ever-decreasing cost for peptide synthesis and the development of collaborative studies among laboratories where many peptide truncations already exist will hopefully enable many more research groups to conduct such additional analyses.

While we strive to collect all well-characterized CTL epitopes in our list of optimally defined CTL epitopes, we are also trying to strike a balance between including as much information and as many epitopes as possible while avoiding the potential detrimental effects of including epitopes that are not conclusively defined. Since most epitopes represent correctly defined optimal targets in a clinically-relevant setting [Goonetilleke *et al.*, 2009], they do put us in the difficult position of either relaxing the inclusion criteria or asking for additional analyses to be conducted. We however also feel that their inclusion in the comprehensive listing (B-list) of the HIV Immunology Database will make such information readily accessible to the wider research community, in the end providing a benefit for all involved in the definition of protective immune responses, T-cell immunity and viral evolution. At the same time, we remain open to suggestions on how we could improve the A-list so that it meets the changing needs of the community. For any comments, please contact us.

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I-A-3 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.*, 2004b
A*0201 (A2)	p17	77–85	SLYNTVATL	Johnson *et al.*, 1991; Parker *et al.*, 1992, 1994
A*0201 (A2)	p2p7p1p6	70–79	FLGKIWPSYK	Yu *et al.*, 2002b
A*0201 (A2)	Protease	76–84	LVGPTPVNI	Karlsson *et al.*, 2003
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	309–317	ILKEPVHGV	Walker *et al.*, 1989; Tsomides *et al.*, 1991
A*0201 (A2)	Vpr	59–67	AIIRILQQL	Altfeld *et al.*, 2001a,b
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)	Nef	136–145	PLTFGWCYKL	Haas *et al.*, 1996; Maier & Autran, 1999
A*0201 (A2)	Nef	180–189	VLEWRFDSRL	Haas *et al.*, 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	RIRQGLERA	Sabbaj *et al.*, 2003
A*0205 (A2)	Nef	83–91	GAFDLSFFL	Rathod, 2006
A*0207 (A2)	p24	164–172	YVDRFYKTL	Currier *et al.*, 2002
A*0301 (A3)	p17	18–26	KIRLRPGGK	Harrer *et al.*, 1996b
A*0301 (A3)	p17	20–28	RLRPGGKKK	Goulder *et al.*, 1997b; Culmann, 1999; Lewinsohn & Riddell, 1999; Wilkes & Ruhl, 1999
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.*, 2001a; 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.*, 1994
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

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

HLA	Protein	AA	Sequence	Reference
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	158–166	AIFQSSMTK	Johnson & Walker, 1994; 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)	Integrase	203–211	IIATDIQTK	Wang *et al.*, 2007
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	134–141	RYPLTFGW	Goulder *et al.*, 1997a; Ikeda-Moore *et al.*, 1998
A*2501 (A25)	p24	13–23	QAISPRTLNAW	Kurane & West, 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
A*2601 (A26)	p24	35–43	EVIPMFSAL	Goulder *et al.*, 1996a
A*2601 (A26)	RT	449–457	ETKLGKAGY	Sabbaj *et al.*, 2003
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*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,b
A*3201 (A32)	RT	392–401	PIQKETWETW	Harrer *et al.*, 1996b
A*3201 (A32)	gp160	419–427	RIKQIINMW	Harrer *et al.*, 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)	gp160	698–707	VFAVLSIVNR	Hossain *et al.*, 2001
A*3303 (A33)	gp160	831–838	EVAQRAYR	Hossain *et al.*, 2001
A*3303 (A33)	Vpu	29–37	EYRKILRQR	Addo *et al.*, 2002
A66	RT	438–448	ETFYVDGAANR	Rathod, 2006
A*6801 (A68)	Tat	39–49	ITKGLGISYGR	Oxenius *et al.*, 2002
A*6801 (A68)	Vpr	52–62	DTWAGVEAIIR	Sabbaj *et al.*, 2004
A*6802 (A68)	RT	436–445	GAETFYVDGA	Rathod & Kiepiela, 2005
A*6802 (A68)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999
A*6802 (A68)	Protease	30–38	DTVLEEWNL	Rowland-Jones, 1999
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 *et al.*, 2002a
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 *et al.*, 1999; Jin *et al.*, 2000; Wilson *et al.*, 1997
B*0702 (B7)	p24	223–231	GPGHKARVL	Goulder, 1999
B*0702 (B7)	Vpr	34–42	FPRIWLHGL	Altfeld *et al.*, 2001a
B*0702 (B7)	Vif	48–57	HPRVSSEVHI	Altfeld *et al.*, 2001a
B*0702 (B7)	gp160	298–307	RPNNNTRKSI	Safrit *et al.*, 1994b
B*0702 (B7)	gp160	843–851	IPRRIRQGL	Wilkes & Ruhl, 1999
B*0702 (B7)	Nef	68–77	FPVTPQVPLR	Haas *et al.*, 1996; Maier & Autran, 1999
B*0702 (B7)	Nef	68–76	FPVTPQVPL	Bauer *et al.*, 1997; Frahm & Goulder, 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*0801 (B8)	p17	24–32	GGKKKYKLK	Reid *et al.*, 1996; Goulder *et al.*, 1997d
B*0801 (B8)	p17	74–82	ELRSLYNTV	Goulder *et al.*, 1997d
B*0801 (B8)	p24	128–135	EIYKRWII	Sutton *et al.*, 1993; Goulder *et al.*, 1997d
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)	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.*, 1997d
B*0801 (B8)	Nef	90–97	FLKEKGGL	Culmann-Penciolelli *et al.*, 1994; Price *et al.*, 1997

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

HLA	Protein	AA	Sequence	Reference
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)	Nef	106–114	RQDILDLWV	Gray *et al.*, 2009
B14	p2p7p1p6	42–50	CRAPRKKGC	Yu *et al.*, 2002b
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 & Kiepiela, 2005
B*1503 (B72)	p24	164–172	YVDRFFKTL	Masemola *et al.*, 2004
B*1503 (B72)	Protease	68–76	GKKAIGTVL	Rathod & Bishop, 2006
B*1503 (B72)	RT	496–505	VTDSQYALGI	Sabbaj *et al.*, 2003
B*1503 (B72)	Integrase	135–143	IQQEFGIPY	Honeyborne & Kiepiela, 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 & Bishop, 2006
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)	Vif	102–111	LADQLIHLHY	Altfeld *et al.*, 2001a
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

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 *et al.*, 1998; Rowland-Jones, 1999
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.*, 1997c
B*2705 (B27)	Integrase	186–194	KRKGGIGGY	Payne & Goulder, 2009
B*2705 (B27)	gp160	786–795	GRRGWEALKY	Lieberman *et al.*, 1992; Lieberman, 1999
B*2705 (B27)	Nef	105–114	RRQDILDLWI	Goulder *et al.*, 1997b
B*3501 (B35)	p17	36–44	WASRELERF	Goulder *et al.*, 1997a
B*3501 (B35)	p17	124–132	NSSKVSQNY	Rowland-Jones *et al.*, 1995
B*3501 (B35)	p24	122–130	PPIPVGDIY	Rowland-Jones *et al.*, 1995
B*3501 (B35)	RT	107–115	TVLDVGDAY	Wilkes & Ruhl, 1999; 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)	gp160	42–52	VPVWKEATTTL	Wilkes & Ruhl, 1999
B*3501 (B35)	gp160	78–86	DPNPQEVVL	Shiga *et al.*, 1996
B*3501 (B35)	gp160	606–614	TAVPWNASW	Johnson *et al.*, 1994
B*3501 (B35)	Nef	74–81	VPLRPMTY	Culmann *et al.*, 1991; Culmann-Penciolelli *et al.*, 1994
B*3701 (B37)	Nef	120–128	YFPDWQNYT	Culmann *et al.*, 1991; Culmann, 1999
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 & West, 1999
B*3910 (B39)	p24	48–56	TPQDLNTML	Honeyborne & Kiepiela, 2005
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)	Nef	92–100	KEKGGLEGL	Sabbaj *et al.*, 2003; Altfeld *et al.*, 2000

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

HLA	Protein	AA	Sequence	Reference
B42	Integrase	28–36	LPPIVAKEI	Kiepiela *et al.*, 2007
B42	Integrase	260–268	VPRRKAKII	Kiepiela & Goulder, 2002
B*4201 (B42)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a
B*4201 (B42)	RT	271–279	YPGIKVRQL	Wilkes & Ruhl, 1999
B*4201 (B42)	Nef	71–79	RPQVPLRPM	Honeyborne, 2006
B*4201 (B42)	Nef	128–137	TPGPGVRYPL	Goulder, 1999
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*4403 (B44)	p17	78–86	LYNTVATLY	Masemola *et al.*, 2004
B*4415 (B12)	p24	28–36	EEKAFSPEV	Bird *et al.*, 2002
B*4501 (B45)	p2p7p1p6	1–10	AEAMSQVTNS	Sabbaj *et al.*, 2004
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)	RT	42–50	EKEGKISKI	Haas *et al.*, 1998; Haas, 1999
B*5101 (B51)	RT	128–135	TAFTIPSI	Sipsas *et al.*, 1997
B*5101 (B51)	gp160	416–424	LPCRIKQII	Tomiyama *et al.*, 1999
B*5201 (B52)	p24	143–150	RMYSPTSI	Wilkes & Ruhl, 1999; Wilson *et al.*, 1997
B53	Nef	135–143	YPLTFGWCF	Kiepiela & Goulder, 2002
B*5301 (B53)	p24	48–56	TPYDINQML	Gotch *et al.*, 1993
B*5301 (B53)	p24	176–184	QASQEVKNW	Buseyne *et al.*, 1996, 1997; Buseyne, 1999
B*5301 (B53)	Tat	2–11	EPVDPRLEPW	Addo *et al.*, 2001
B*5301 (B53)	Nef	135–143	YPLTFGWCY	Sabbaj *et al.*, 2003
B*5501 (B55)	gp160	42–51	VPVWKEATTT	Shankar *et al.*, 1996; Lieberman, 1999

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

HLA	Protein	AA	Sequence	Reference
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 & Rathod, 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.*, 1996b
B*5701 (B57)	p24	30–40	KAFSPEVIPMF	Goulder *et al.*, 1996b
B*5701 (B57)	p24	108–117	TSTLQEQIGW	Goulder *et al.*, 1996b
B*5701 (B57)	p24	176–184	QASQEVKNW	Goulder *et al.*, 1996b
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.*, 1996b; Hay, 1999
B*5701 (B57)	Vpr	30–38	AVRHFPRIW	Altfeld *et al.*, 2001a
B*5701 (B57)	Vif	31–39	ISKKAKGWF	Altfeld *et al.*, 2001a
B*5701 (B57)	Rev	14–23	KAVRLIKFLY	Addo *et al.*, 2001
B*5701 (B57)	Nef	116–125	HTQGYFPDWQ	Culmann *et al.*, 1991
B*5701 (B57)	Nef	120–128	YFPDWQNYT	Culmann *et al.*, 1991
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)	Nef	83–91	AAFDLSFFL	Gray *et al.*, 2009
B58	p17	76–86	RSLYNTVATLY	Frahm *et al.*, 2005
B58	Tat	2–11	EPVDPRLEPW	Frahm & Brander, 2005
B58	gp160	59–69	KAYETEVHNVW	Rathod & Bishop, 2006
B*5801 (B58)	p24	108–117	TSTLQEQIGW	Goulder *et al.*, 1996b; Bertoletti *et al.*, 1998
B*5801 (B58)	RT	375–383	IAMESIVIW	Kiepiela & Goulder, 2002
B*5801 (B58)	Rev	14–23	KAVRLIKFLY	Addo *et al.*, 2001
B62	Nef	19–27	RMRRAEPAA	Cao, 2002
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
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.*, 2001a

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

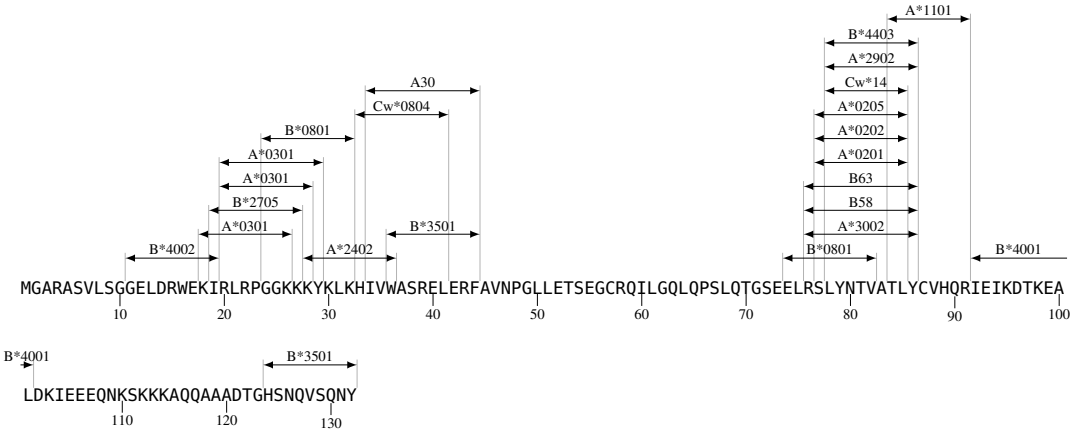
HLA	Protein	AA	Sequence	Reference
Cw1	gp160	218–226	CAPAGFAIL	Zuñiga, 2008; Streeck *et al.*, 2008
Cw*0102 (Cw1)	p24	36–43	VIPMFSAL	Goulder *et al.*, 1997a
Cw*0102 (Cw1)	Gag-Pol TF	24–31	NSPTRREL	Liu *et al.*, 2006
Cw3	Nef	83–91	AALDLSHFL	Draenert *et al.*, 2004b
Cw*0303 (Cw9)	p24	164–172	YVDRFFKTL	Honeyborne, 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
Cw*0501	Rev	67-75	SAEPVPLQL	Addo *et al.*, 2001
Cw6	Nef	120–128	YFPDWQNYT	Frahm & Brander, 2005
Cw7	Nef	105–115	KRQEILDLWVY	Kiepiela & Goulder, 2002; Yu *et al.*, 2002a
Cw8	gp160	557–565	RAIEAQQHM	Bishop & Honeyborne, 2006
Cw8	Nef	82–91	KAAVDLSHFL	Harrer *et al.*, 1996b
Cw*0802 (Cw8)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a; Honeyborne & Kiepiela, 2005
Cw*0802 (Cw8)	RT	495–503	IVTDSQYAL	Rathod & Honeyborne, 2006
Cw*0802 (Cw8)	Nef	83–91	AAVDLSHFL	Cao *et al.*, 2003; Rathod & Honeyborne, 2006
Cw*0804 (Cw8)	p17	33–41	HLVWASREL	Masemola *et al.*, 2004
Cw12	Tat	30–37	CCFHCQVC	Cao *et al.*, 2003; Nixon *et al.*, 1999
Cw14	p17	78–85	LYNTVATL	Horton & Havenar-Daughton, 2005
Cw15	gp160	557–565	RAIEAQQHL	Trocha, 2002
Cw18	p24	142–150	VRMYSPVSI	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

Reviews

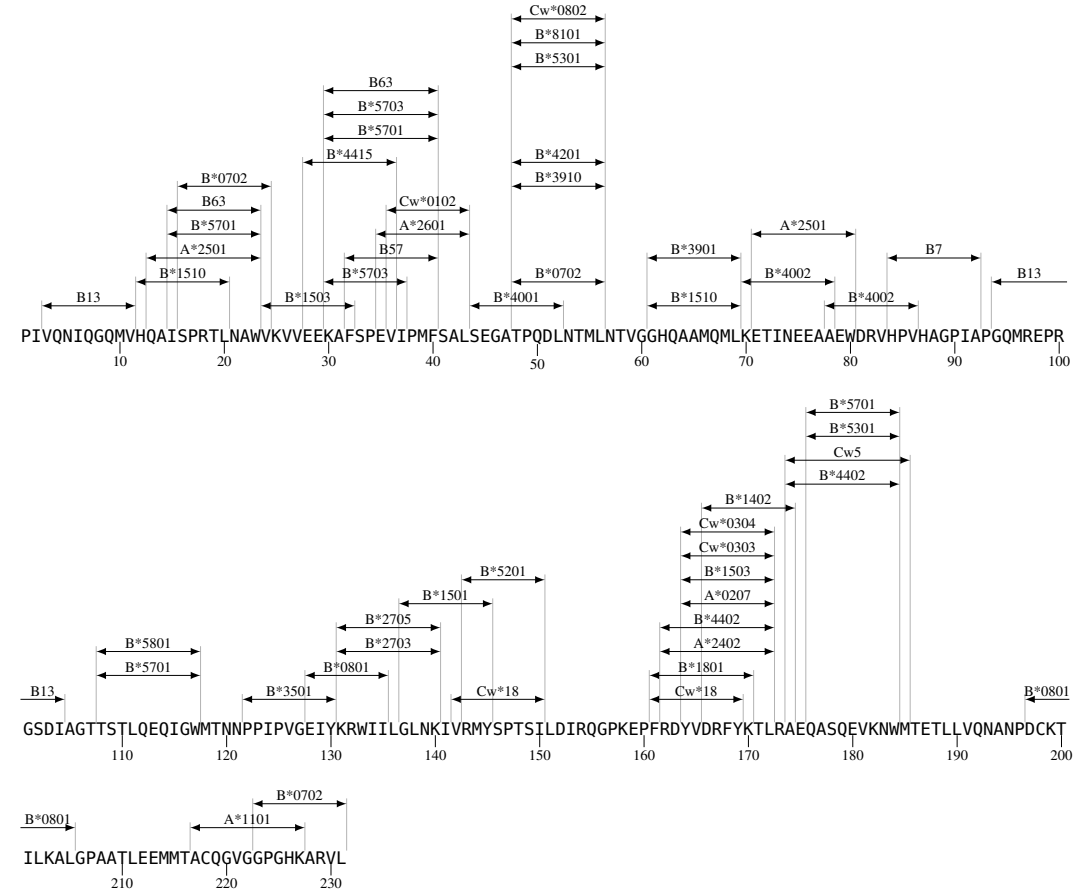
I-A-4 Map of optimal HIV-1 CTL epitopes

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.

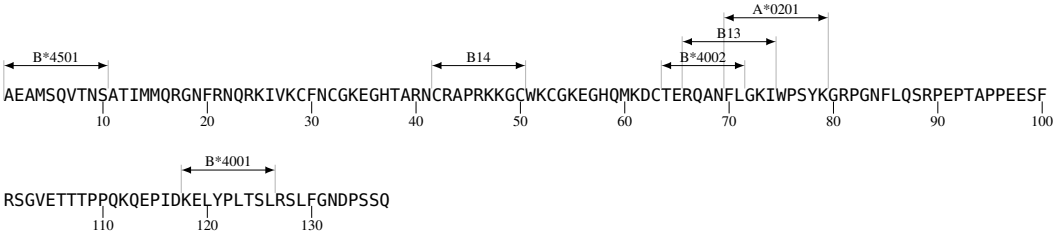
p17 Optimal CTL Epitope Map



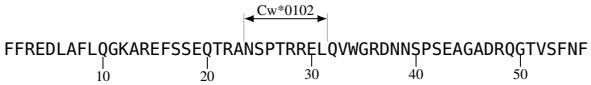
p24 Optimal CTL Epitope Map



p2p7p1p6 Optimal CTL Epitope Map

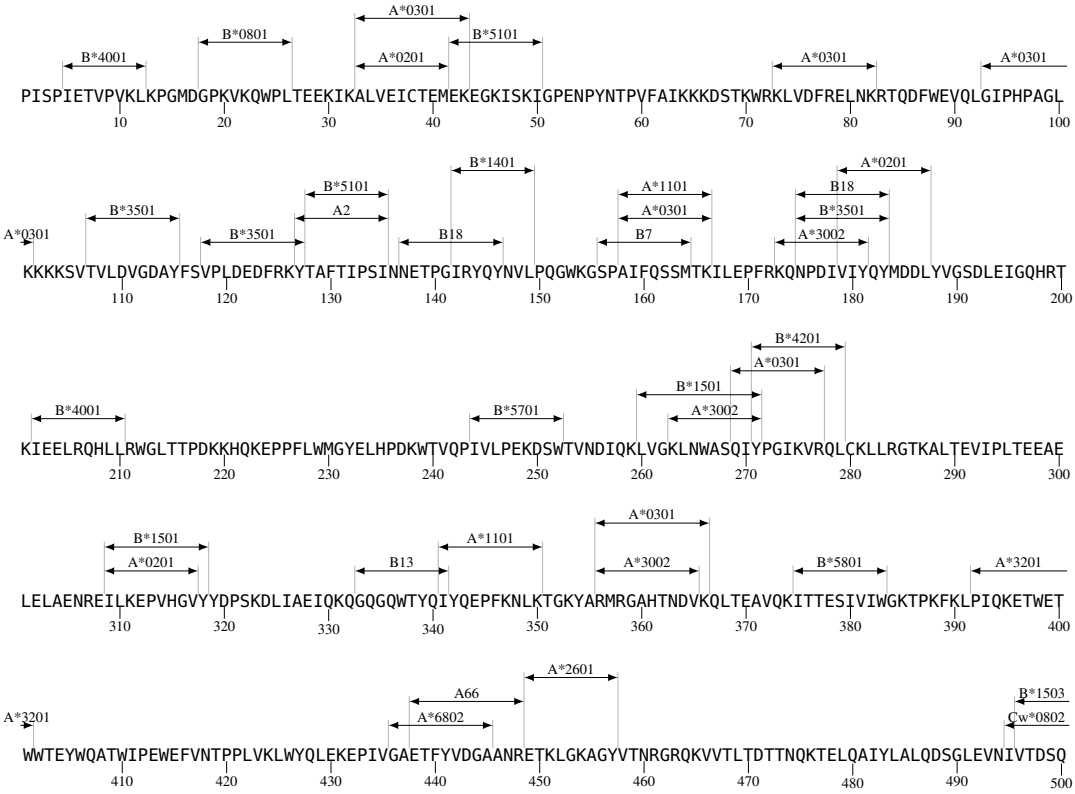


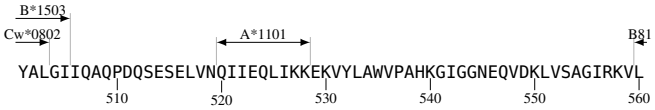
Gag/Pol TF Optimal CTL Epitope Map



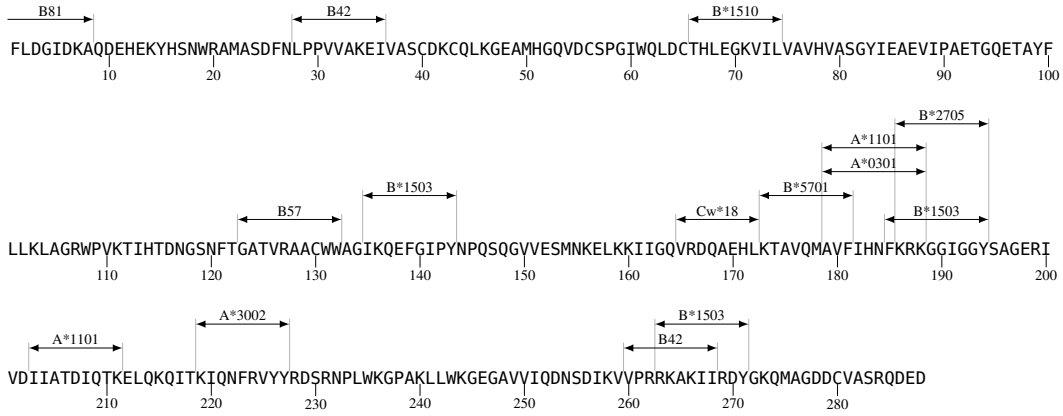
Protease Optimal CTL Epitope Map

RT Optimal CTL Epitope Map

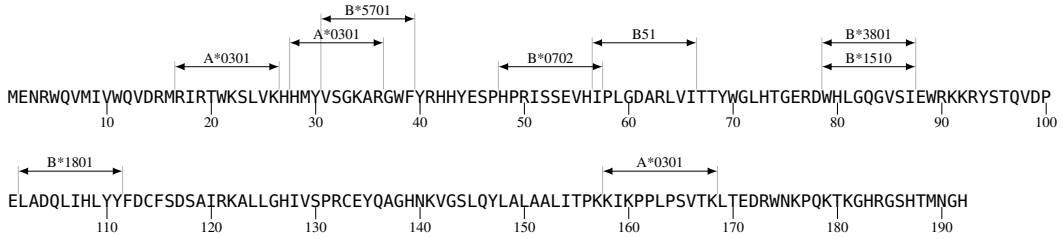




Integrase Optimal CTL Epitope Map

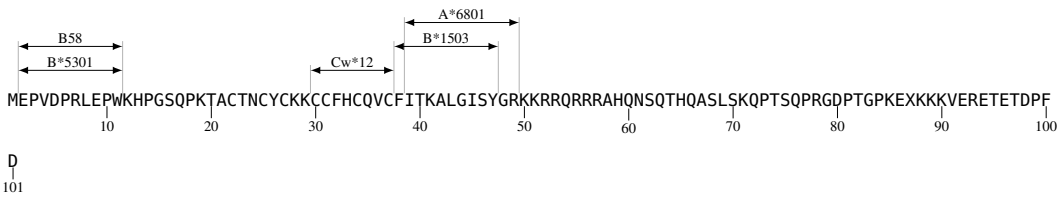


Vif Optimal CTL Epitope Map

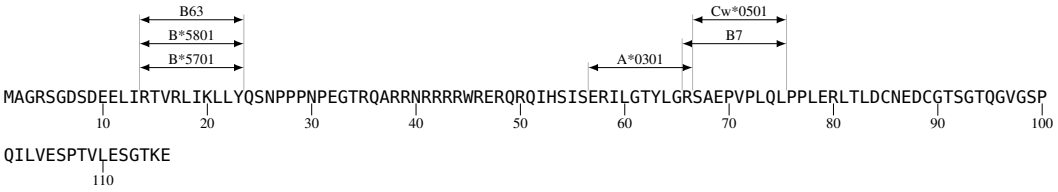


Vpr Optimal CTL Epitope Map

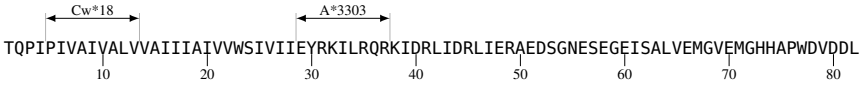
Tat Optimal CTL Epitope Map



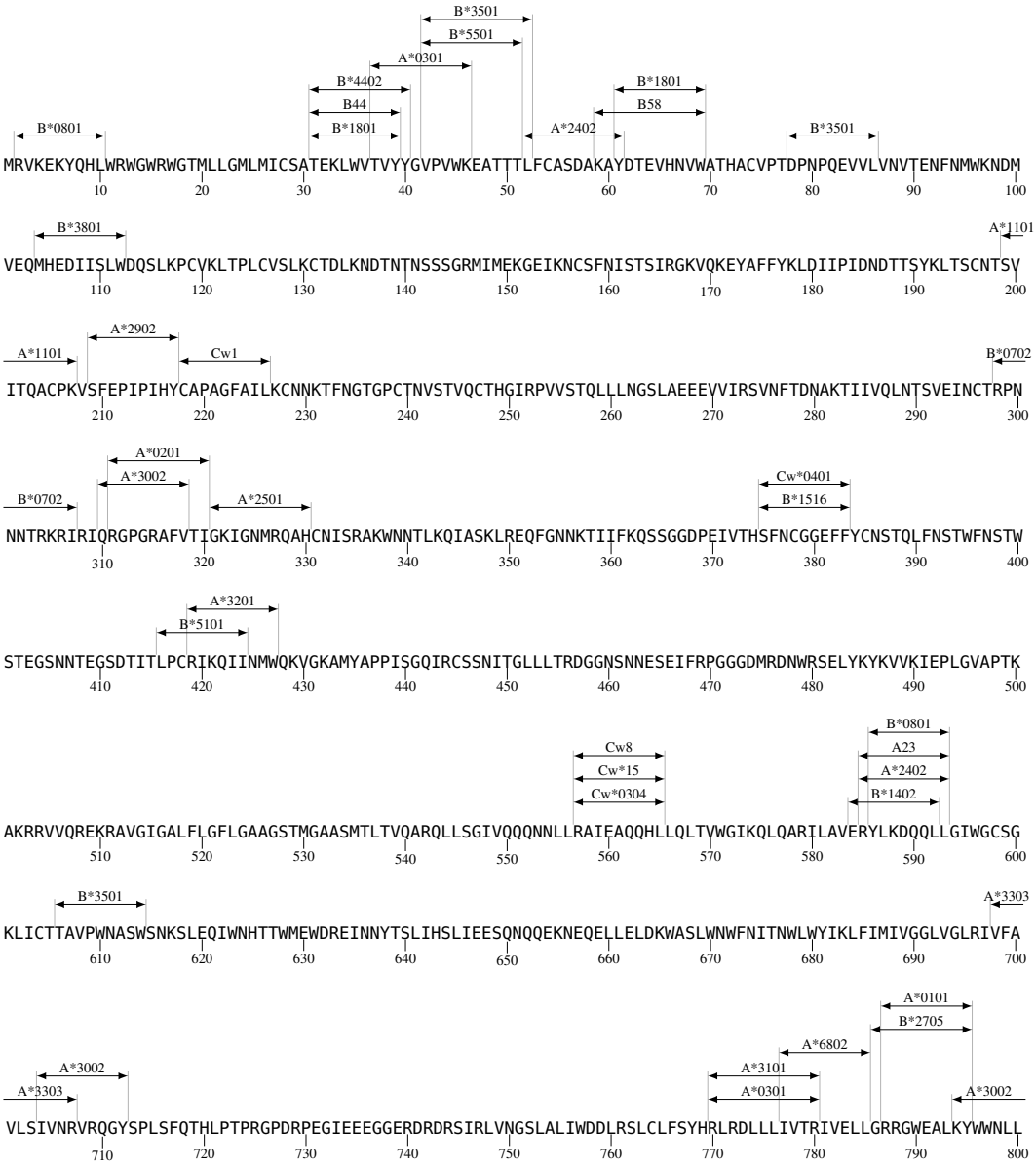
Rev Optimal CTL Epitope Map



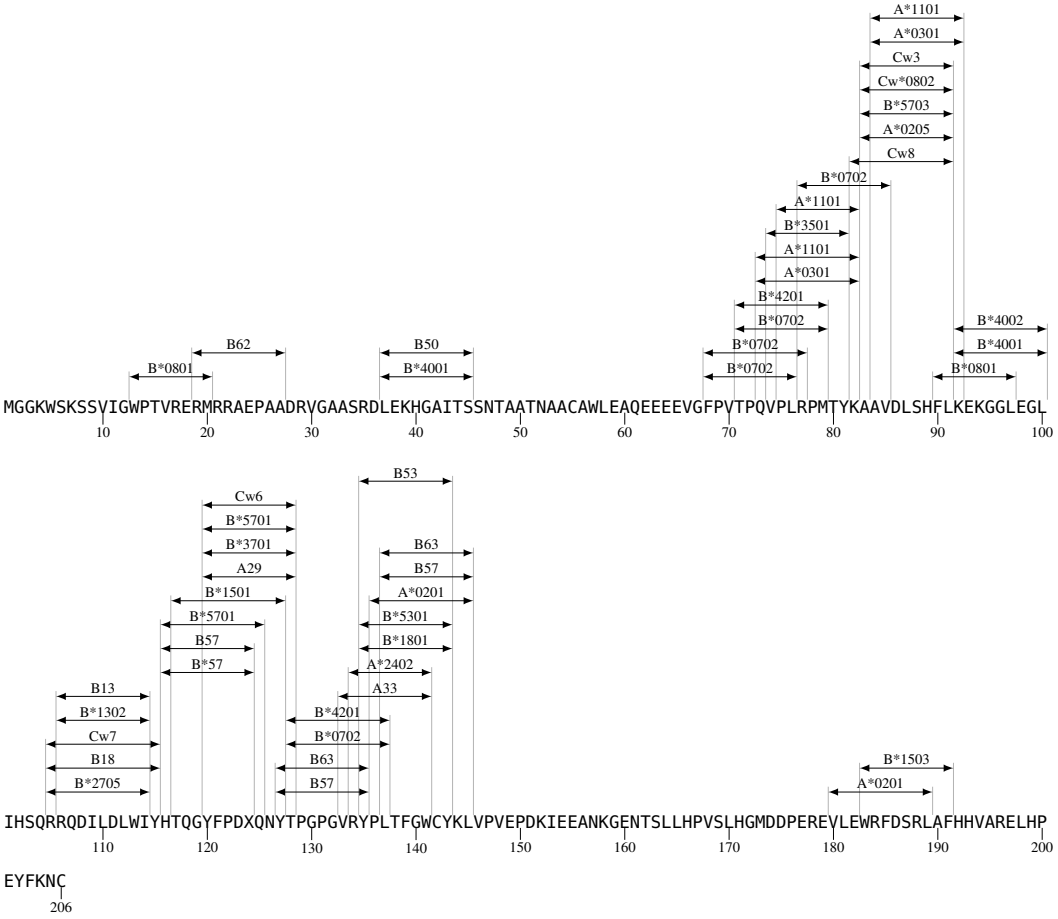
Vpu Optimal CTL Epitope Map



gp160 Optimal CTL Epitope Map



Nef Optimal CTL Epitope Map



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