I-A

Identification and Optimal Definition of HIV-Derived Cytotoxic T Lymphocyte (CTL) Epitopes for the Study of CTL Escape, Functional Avidity and Viral Evolution

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I-A-1 Associations between T cell specificity and viral control: cause or effect?

Despite ongoing efforts into the characterization of immune correlates of controlled HIV infection, the impact of antigen specificity, viral sequence variation and variant cross-recognition on the control of viral replication and HIV disease progression remains unknown. While a steadily growing number of reports confirm the association between T cell responses directed against the HIV Gag protein and reduced viral load [Zuñiga *et al.*, 2006; Brumme *et al.*, 2008; Kiepiela *et al.*, 2007; Masemola *et al.*, 2004a; Rolland *et al.*, 2008], and despite some reports showing a rapid re-presentation of Gag-derived antigen from the incoming virus [Sacha *et al.*, 2007], it remains unclear whether a) these associations reflect the cause or the consequences of otherwise controlled infection and b) whether, and if so, which regions outside of Gag would present effective targets of the host cellular immune response to HIV. Similarly, although a number of recent reports have established strong associations between reduced viral replicative fitness and specific viral sequence changes in Gag epitopes restricted by HLA alleles associated with relative protection [Brockman *et al.*, 2007; Schneidewind *et al.*, 2007; Martinez-Picado *et al.*, 2006], these analyses urgently need to be expanded to other, broadly distributed HLA alleles and targets located in viral proteins other than Gag. In addition, the consequences of sequence variation on T cell recognition, often assumed to reflect effective T cell escape, will need to be more carefully assessed, ideally including approaches such as viral inhibition assays and testing for different T cell effector functions to discriminate between partial agonistic variants, antagonistic or superagonistic sequence changes, or true CTL escape due to abrogated HLA binding, missing TCR interaction or severely impaired antigen processing.

I-A-2 The role of functional avidity in the control of highly variable pathogens

A rapidly growing number of reports have also started to assess the role of T cell receptor repertoire diversity, TCR functional avidity and variant recognition [Price *et al.*, 2005; Turnbull *et al.*, 2006; Messaoudi *et al.*, 2002]. Recently published data in HCV infection has linked the presence of T cell responses of high functional avidity with a superior ability to cross-react with sequence variants [Yerly *et al.*, 2008]. Although these high avidity HCV-specific T cell populations were mainly found in subjects that spontaneously cleared HCV infection, it remains unclear whether individuals who went on to become chronically infected initially also had such high avidity responses which, for unknown reasons, got lost over time, similarly to what has recently been described in longitudinal analyses in HIV infection. Emerging data in HIV infection confirms the analyses in HCV as Frahm *et al.* (unpublished data) and likely others have identified particularly highly avid and broadly cross-reactive T cell populations in HIV controllers, but less so in individuals with progressive HIV disease. It thus appears likely that an effective HIV vaccine (and HCV, too) would likely profit from the induction of such high avidity responses.

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I-A-3 Refined HLA footprint analyses and the identification of novel CTL epitopes and HLA binding motifs

Aside from determining the roles of functional avidity and TCR repertoires, the analysis of viral evolution as a consequence of cytotoxic T lymphocyte (CTL) mediated immune pressure has given rise to a flurry of publications over the last few years [Moore *et al.*, 2002; McMichael & Klenerman, 2002]. Since the initial description of these HLA footprints in the HIV sequence, refined approaches have now been developed that take into consideration potentially confounding effects of the phylogeny of the analyzed sequences and HLA linkage disequilibrium [Brumme *et al.*, 2008; Bhattacharya *et al.*, 2007; Brumme *et al.*, 2007]. These analyses have also allowed for the identification of novel T cell epitopes by a sort of a "reversed" genetic approach that points towards the existence of novel T cell epitopes at or close to sites of strong associations between specific HLA alleles and recurrent viral sequence polymorphisms. With larger cohorts being generated and comprehensively analyzed in different geographic regions of the world with populations of considerably different host genetics and circulating viral populations, such HLA footprint analyses now also allow to assess the global effects of viral adaptation to HLA restricted T cell mediated immune pressure [Rousseau *et al.*, 2008]. Taking into consideration the balancing effects of forward mutations and reversion to pre-infection sequence, large cohort based analyses, together with detailed *in vitro* viral fitness studies, may also allow to determine the relative strength of the CTL mediated immune pressure and the effectiveness of an epitope specific CTL response. Especially for these kinds of studies, however, it is necessary to define the precise epitope so that the effectiveness of CTL escape and its potential different mechanisms (processing escape versus abrogated HLA binding, etc.) can correctly be assessed.

With more studies moving into populations where less well-characterized HLA alleles are more prevalent, epitope definition becomes more difficult (due to less well known binding motifs for instance) but also more informative for the relevant populations. Especially for such less well characterized alleles, the inference of binding motifs and subsequent identification of optimal epitopes through the analysis of HLA sequence positions lining the binding pockets has proven quite effective [Honeyborne *et al.*, 2007; Frahm *et al.*, 2005, 2006]. At the same time, our own analyses on promiscuously presented HIV epitopes clearly indicate that the current description of allele-specific motifs is still incomplete, and that the identification of truly optimally defined epitopes, viral or not, will help to amend and more accurately define existing binding motifs [Frahm *et al.*, 2007]. This would obviously not only facilitate the work in HIV but also in other viral infections, cancer and autoimmunity.

I-A-4 Are current criteria for the definition of "optimal" epitopes helpful to the community

As in past years, the present listing is based on the inclusion of epitopes that fulfill a number of criteria intended to ensuring reliable description of the optimal length epitope and correct assignment of the restricting HLA class I allele(s) [Brander & Walker, 1995, 1996]. Nevertheless, there may still be occasions where the data reported here conflict with data in other laboratories and we would like to encourage any investigator who observes discrepancies in his/her own data with what is reported here to bring this to our attention. In addition, we have still adhered to the previously described inclusion criteria, being aware that some epitopes may fail one or more of these tests although they may indeed represent optimal epitopes [Schellens *et al.*, 2008; Mueller *et al.*, 2007]. In particular, we and others are moving towards the use of single HLA allele transfected cell lines for HLA restriction analyses. While this approach would seemingly define the presenting allele directly, it is possible that stabilization of the allele on the cell surface may be sufficient to trigger a response, even though the allele is not the truly restricting one. We would thus like to suggest that each class I allele expressed by the subject from whom the effector cells were obtained be tested, either as single allele expressing cell lines or as a negative control antigen presenting cell line that matches as many of the presumably non-restricting alleles as possible. Alternatively, a known good binding epitope different from the one that is to be mapped could be used to exclude unspecific reaction due to high peptide concentration in the assay. High peptide concentration may also be a factor for the elicitation of responses in the Elispot assay that are however unable to inhibit viral replication [Valentine *et al.*, 2008]. While such cases may indeed identify epitopes with likely little contribution to effective viral control *in vivo*, their identification is still necessary to allow for their exclusion from potential immunogen sequences.

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 *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	703–712	EIIFDIRQAY	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.*, 2004b
A*2902 (A29)	gp160	209–217	SFEPIPIHY	Altfeld, 2000
A30	p17	34–44	LVWASRELERF	Masemola *et al.*, 2004b
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	41–50	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	106–115	RQDILDLWIY	Goulder, 1999
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
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.*, 2004b
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	WHLGHVSI	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)	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.*, 2004b
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)			2 C **I** **V** Q	Rammensee *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
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

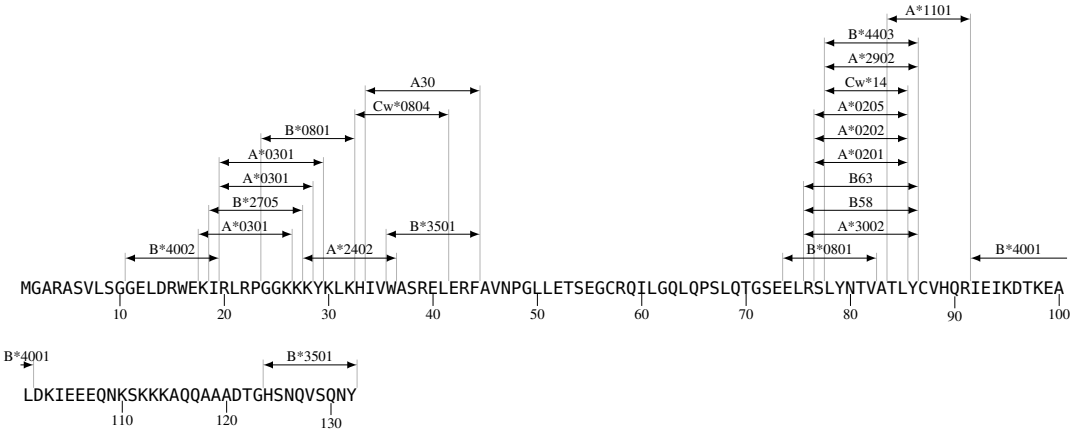
Table I-A-1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
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.*, 2004b
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	gp160	511–519	YRLGVGALI	Honeyborne, 2006

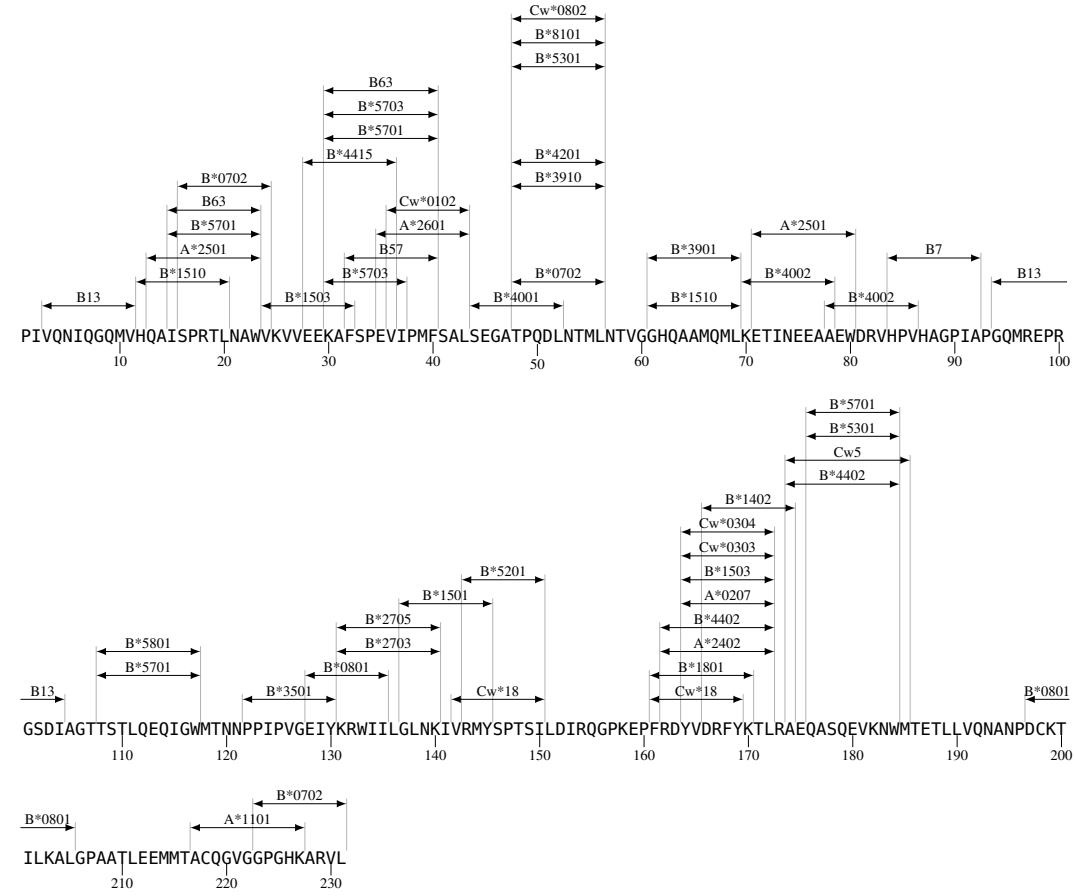
I-A-6 Map of optimal HIV-1 CTL epitopes

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.

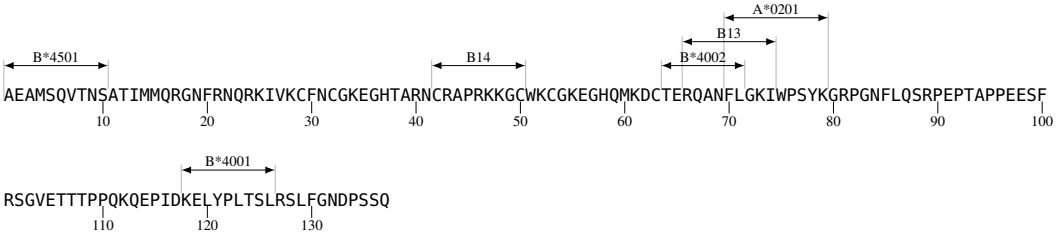
p17 Optimal CTL Epitope Map



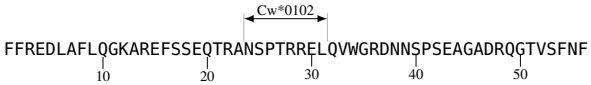
p24 Optimal CTL Epitope Map



p2p7p1p6 Optimal CTL Epitope Map

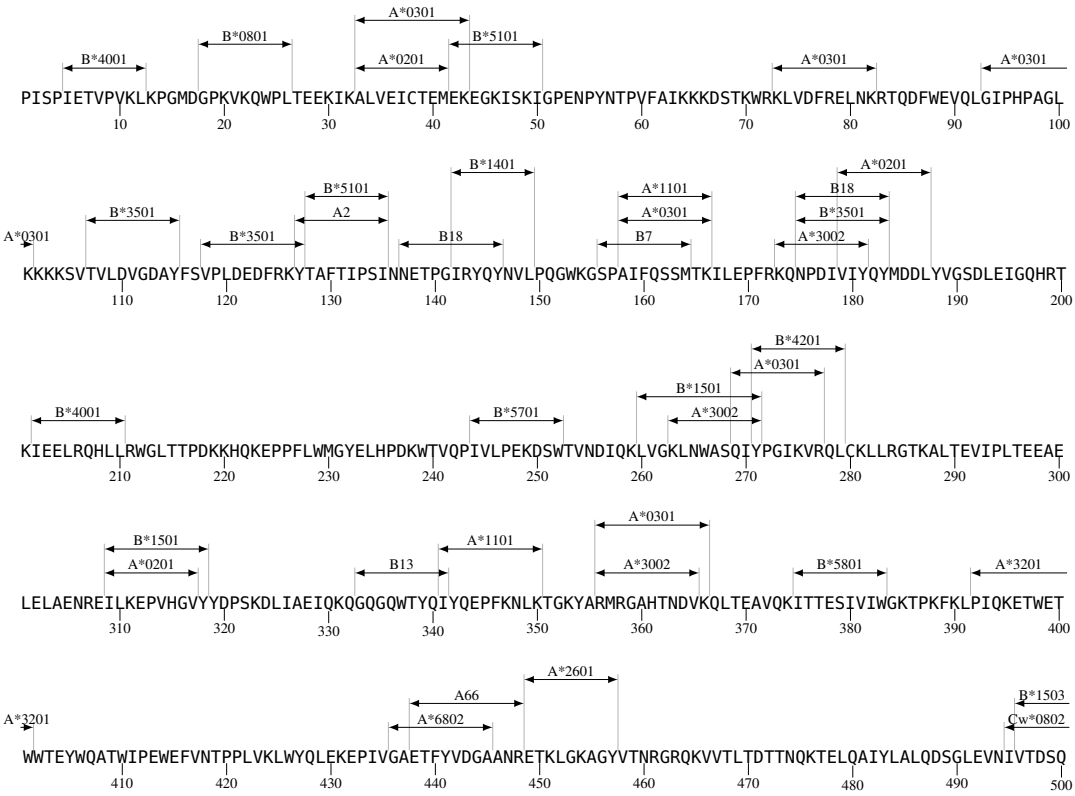


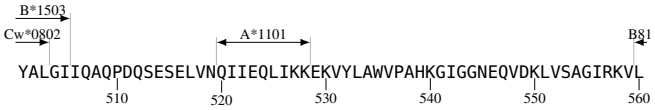
Gag/Pol TF Optimal CTL Epitope Map



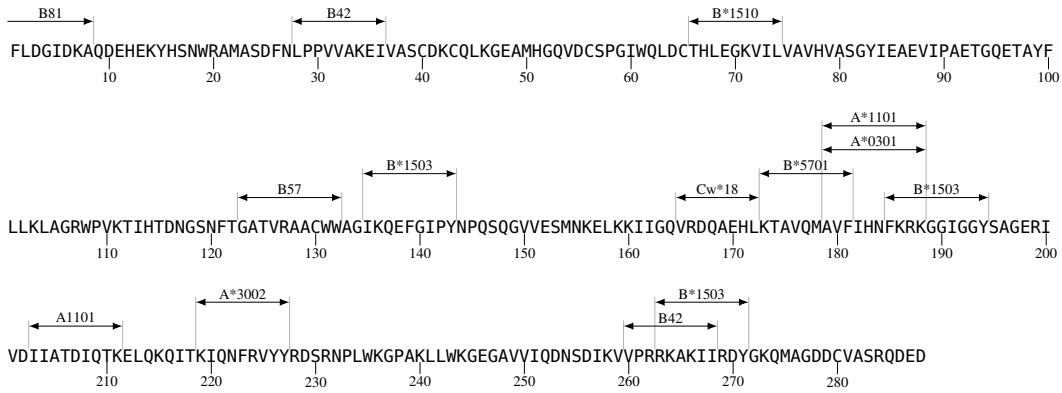
Protease Optimal CTL Epitope Map

RT Optimal CTL Epitope Map

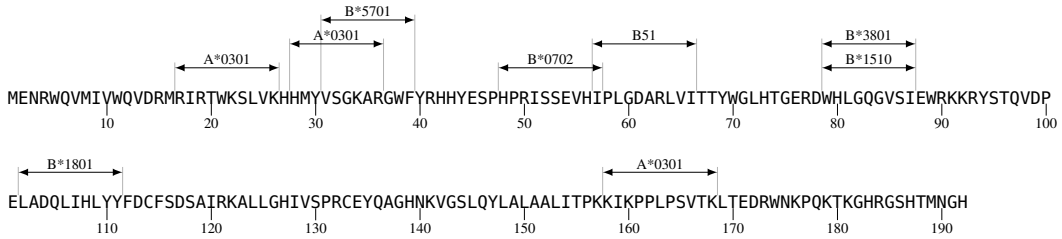




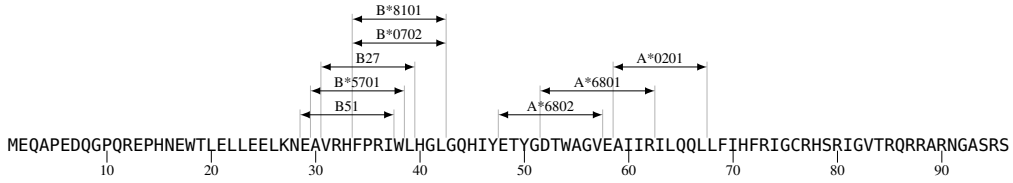
Integrase Optimal CTL Epitope Map



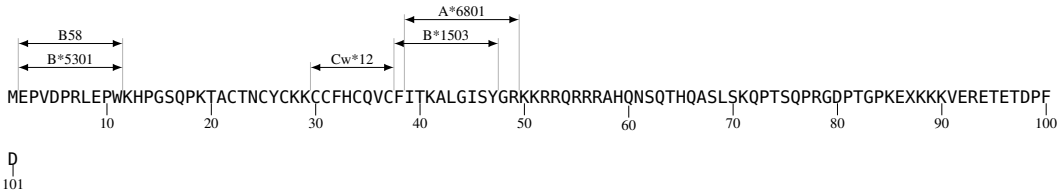
Vif Optimal CTL Epitope Map



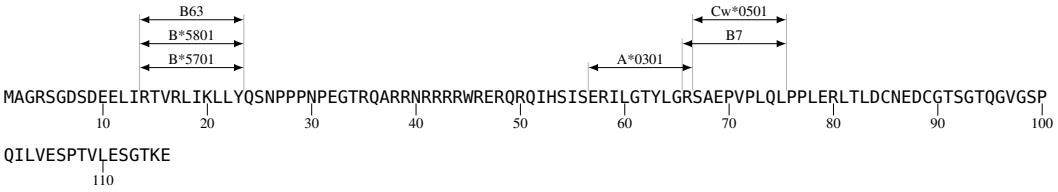
Vpr Optimal CTL Epitope Map



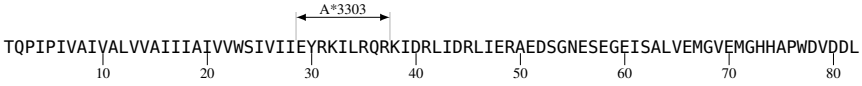
Tat Optimal CTL Epitope Map



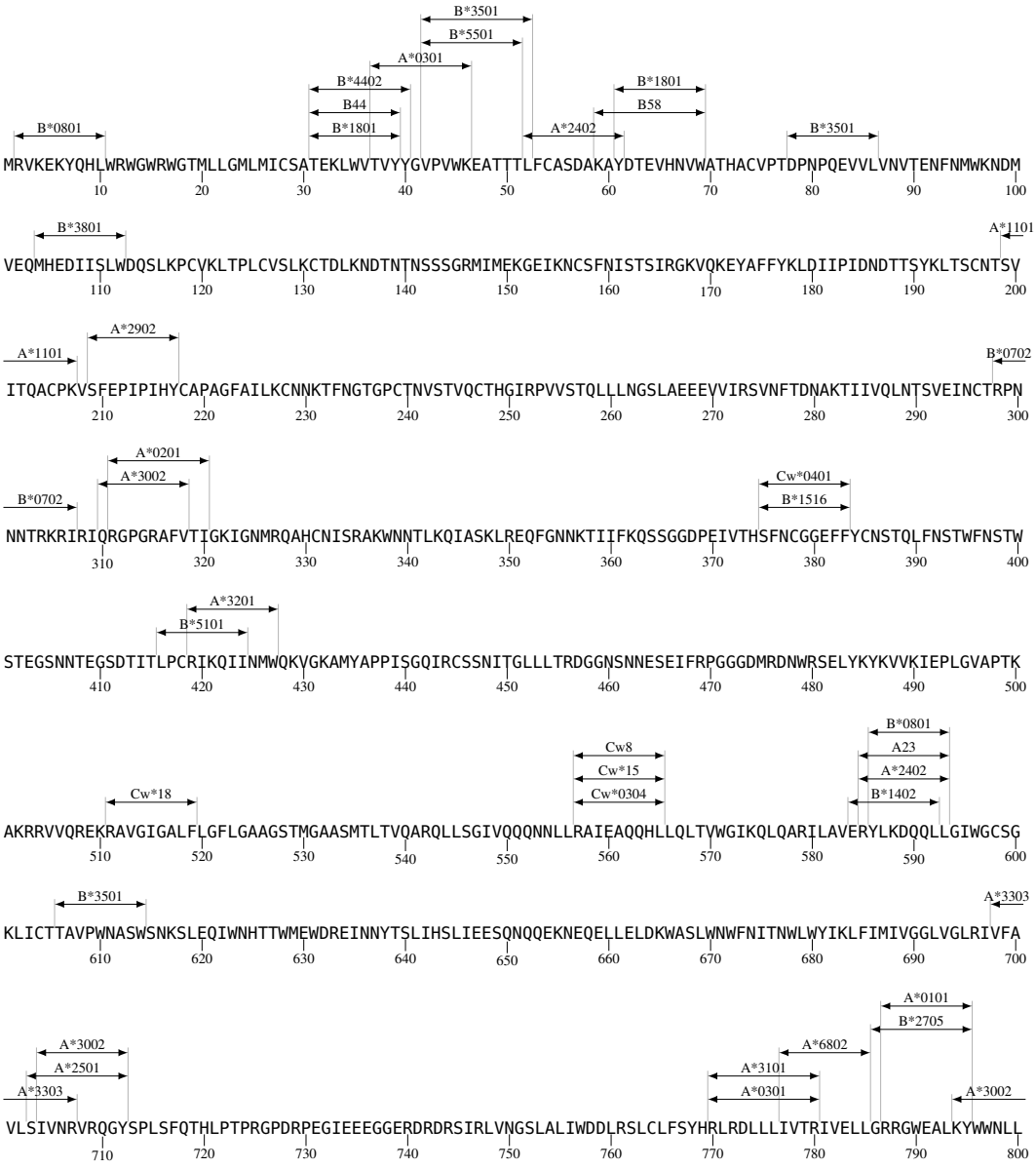
Rev Optimal CTL Epitope Map



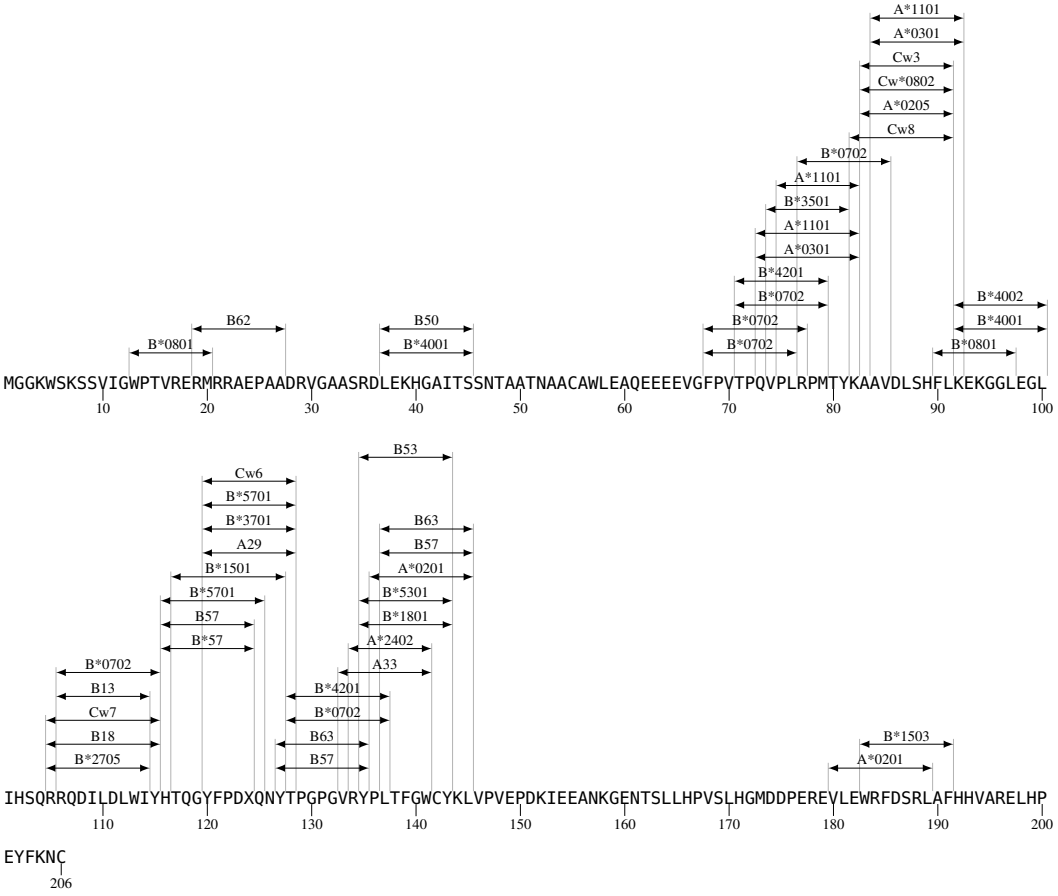
Vpu Optimal CTL Epitope Map



gp160 Optimal CTL Epitope Map



Nef Optimal CTL Epitope Map



I-A-7 Acknowledgments

We would like to express our gratitude to the large number of researchers in the field who continuously contribute to this database. We very much welcome any criticism, comments and additions to this list since we are sure that some epitopes will unintentionally escape our attention, despite close monitoring of the literature. Also, we would like to especially invite suggestions as to the use of alternative or additional selection criteria to define optimal epitopes as we strive to make this listing as extensive and useful to the community as possible, while maintaining its integrity. Please write or call us with any comments you may have at:

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