I-A

Identification of HIV-Derived, HLA Class I Restricted CTL Epitopes: Insights into TCR Repertoire, CTL Escape and Viral Fitness

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I-A-1 The importance of well-defined T cell epitopes in understanding host immunity to HIV

A detailed understanding of T cell immunity to HIV infection will be required for the design and development of an effective HIV vaccine. Over the last few years, it has become clear that the mere breadth and magnitude of T cell responses directed against the entire viral proteome are not associated with immune control and that a more in-depth look at T cell specificity, effector functions and viral diversity will be needed to define true correlates of immune protection [Zuñiga *et al.*, 2006; Frahm *et al.*, 2004; Kiepiela *et al.*, 2004; Betts *et al.*, 2006; Masemola *et al.*, 2004a]. In particular, the relationship between targeting specific regions of the viral genome, T cell escape and, as a consequence, changes in viral replicative fitness has become a focus of much debate [Zuñiga *et al.*, 2006; Masemola *et al.*, 2004a; Martinez-Picado *et al.*, 2006; Bailey *et al.*, 2006; Li *et al.*, 2007; Liu *et al.*, 2006; Yeh *et al.*, 2006; Ganusov & De Boer, 2006]. In addition, studies on both the transmission and reversion of CTL escape variants, the induction of T cell specificities against effective viral escape variants as well as work addressing the role of subdominant T cell responses in the control of HIV have provided a better understanding of the complex dynamics between host immune response and viral adaptation to immune pressure [Leslie *et al.*, 2004, 2005; Friedrich *et al.*, 2004; Allen *et al.*, 2005b,a; Frahm *et al.*, 2006a]. For most of these studies, the identification of precisely defined HLA class I-restricted CTL epitopes has been key and will continue to be a central prerequisite, especially in studies that focus on less well studied human populations with diverse HLA backgrounds [Kiepiela *et al.*, 2004].

I-A-2 Escape pathways of dominant CTL epitopes

Despite the increasing appreciation for the role of subdominant CTL responses in viral control, much of the current knowledge on immune driven viral evolution and CTL escape is based on the study of a few, well defined, dominant T cell targets [Bailey *et al.*, 2006; Leslie *et al.*, 2004, 2005; Frahm *et al.*, 2006a; Brander *et al.*, 1998; Iversen *et al.*, 2006; Migueles *et al.*, 2003; Yu *et al.*, 2006]. In some of these cases, for instance the dominant HLA-B27-restricted epitope KK10 in HIV Gag p24 (KRWIILGLNK), CTL escape from a single epitope can result in elevated viral loads and accelerated disease progression [Goulder *et al.*, 1997c; Feeney *et al.*, 2004]. However, for other epitopes and alleles, the relationship between CTL escape and disease progression may be more complex. For instance, in the case of the HLA-B57-restricted KF11 epitope (KAFSPEVIPMF), a number of studies have found intact viral epitope sequences and significant epitope-specific responses even in individuals with seemingly uncontrolled viral replication [Migueles *et al.*, 2003]. On the other hand, others have reported "escape" mutations in the KF11 epitope in individuals with elite control of viral replication [Bailey *et al.*, 2006], indicating that additional factors are likely crucially involved in shaping an effective T cell response to this virus. Indeed, recent data generated by multi-color flow cytometric analyses highlight the importance of polyfunctional effector cells in the control of HIV. These polyfunctional T cells may be impaired in some individuals with progressive disease , although these subjects may have conserved epitope sequences and strong, epitope-specific T cell responses as assessed by interferon-γ secretion [Betts *et al.*, 2006].

A number of reports have now also begun to address the kinetics of compensatory mutations that are either required for effective T cell escape or for the maintenance of viral replicative fitness [Yeh *et al.*, 2006; Iversen *et al.*, 2006; Kelleher *et al.*, 2001; Peyerl *et al.*, 2004]. Recent

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analyses by Iversen *et al.* [2006] have addressed viral escape pathways in the context of the dominant HLA-A2 restricted epitope SLYNTVATL in HIV Gag p17, showing that effective viral escape was only achieved after serial mutations in three positions within the optimal epitope. These changes were required for escape from TCR recognition, indicating that simple reduction of epitope binding affinity to the presenting HLA class I molecule does not necessarily allow the virus to evade immune control. Rather, effective escape may occur only when there is a profoundly diminished interaction between TCR and the HLA/peptide complex, to which the epitope binding affinity will only partially contribute. This highlights the need to expand the analyses of HIV-specific immune responses to include detailed assessments of functional avidity of these responses as well as to consider the impact that the T cell receptor repertoire diversity may have on the emergence of CTL escape variants. Thus, a number of studies have started to shed some light on the factors that define a broadly cross-reactive and highly avid T cell response, which may be especially well suited to prevent viral escape. Of note, a number of recent analyses have indicated that a more narrow T cell receptor repertoire, mediating T cell responses of high functional avidity, may be particularly effective in controlling viral replication [Yu *et al.*, 2006; Price *et al.*, 2004; Frahm *et al.*, 2006b; Ahlers *et al.*, 2001; Alexander-Miller *et al.*, 1996a]. Although one might expect a broader epitope-specific TCR repertoire to provide more possible candidate TCR to effectively recognize emerging escape variants, our own data and studies from other laboratories indicate that an increased breath of the TCR repertoire may be associated with reduced functional avidity of the total epitope-specific T cell population [Yu *et al.*, 2006; Price *et al.*, 2004; Frahm *et al.*, 2006b; Messaoudi *et al.*, 2002]. This is highlighted in a recent analysis of the TCR usage in T cells directed against the dominant HIV Gag KF11 (KAFSPEVIPMF) epitope, which can be restricted by the two closely related alleles HLA-B*5701 and B*5703. In the context of HLA-B*5701, the KF11 specific response is characterized by a TCR repertoire that is highly conserved among HLA-B*5701-expressing individuals and that efficiently cross-reacts with viral epitope variants [Yu *et al.*, 2006]. In contrast, in the context of HLA-B*5703, the KF11 epitope induces an entirely different, more heterogeneous TCR repertoire that fails to recognize the most frequently occurring epitope variants, indicating that extensive TCR diversity may not effectively prevent the emergence of epitope escape variants. How the immune system may control the emergence of highly avid rather than broad TCR repertoires may at least partly depend on antigen availability and competition of expanding T cell populations [Kim *et al.*, 2006; Price *et al.*, 2005]. Studies that address these factors in HIV and other viral infections will have obviously important implications for vaccine design, which may need to consider different levels of antigen availability during the induction phase of responses and aim to specifically drive the expansion of high avidity T cell responses of limited TCR diversity and (thus) superior ability to recognize epitope variants.

I-A-3 Inclusion of epitopes in the optimal list

As every year, the present listing is based on the inclusion of epitopes that fulfill a number of stringent criteria intended to ensure reliable description of the optimal length epitope and correct assignment of the restricting HLA class I allele(s) [Hunziker *et al.*, 1998; Brander & Walker, 1995]. Nevertheless, there may still be occasions where the data reported here conflict with data in other laboratories and we to encourage any investigators who observe discrepancies in their own data and what is reported here to bring this to our attention. The selection of inclusion criteria itself is obviously subject to potential disagreement, too. In particular, a number of epitopes have been described over the last year where binding motif algorithms have been used to predict the optimal epitope length, or for which the restricting HLA class I alleles have been inferred by statistical associations or binding assays [Kawashima *et al.*, 2005; Satoh *et al.*, 2005]. Although in some large cohort analyses, a number of associations have reached statistically highly significant associations, the optimal epitope was often inferred based on previously published motif data [Kiepiela *et al.*, 2004; Honeyborne *et al.*, 2006]. We have thus opted not include these epitopes even though a number of them are likely to be accurately described. However, as binding motif predictions are only as good as the quality of the described epitopes for a given allele, care must be taken to not further "confirm" existing binding motifs by data that were generated based on the original training set defining the motifs in the first place. Thus, at least some of the inferred optimal epitope lengths should ideally be confirmed experimentally to ensure that sometimes only loosely defined allele-specific binding motifs are indeed correct. Thus, while newly identified epitopes may violate known HLA binding motifs, these extensively mapped epitopes may help to refine currently incompletely defined allele-specific binding motifs. The expansion of binding motifs to include less frequently used amino acids will not only facilitate work in the HIV field, but also in other viral infections, cancer and autoimmunity.

I-A-4 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, 2004
A*0201 (A2)			2 6 C	Falk *et al.*, 1991; Barouch *et al.*, 1995
		1° anchor	**L** **L**	
			M **V**	
		2° anchor	V	
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.*, 1996b
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)			2 C	Barouch *et al.*, 1995
			L **L**	
			V	
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

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

HLA	Protein	AA	Sequence	Reference
A*0301 (A3)			2 C **L** **K** **V** **Y** **M** I F A R S T	Marsh *et al.*, 2000
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
A*1101 (A11)			2 C **K** V I F Y	Zhang *et al.*, 1993; Rammensee *et al.*, 1995
A*1101 (A11)	p17	84–92	TLYCVHQRI	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)	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

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

HLA	Protein	AA	Sequence	Reference
A*2402 (A24)			2 C **Y** **I** **L** **F**	Maier *et al.*, 1994
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)			12 6 C **V** **Y** **T** **F** **I** **L** **F** D I E L V	Dumrese *et al.*, 1998
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.*, 2004
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)			12 C **Y** **Y** **F** **L** **V** R	Rammensee *et al.*, 1999
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

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

HLA	Protein	AA	Sequence	Reference
A*3101 (A31)			2 C **R** L V Y F	Falk *et al.*, 1994; Rammensee *et al.*, 1999
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
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

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

HLA	Protein	AA	Sequence	Reference
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)			123 C **P** **L** A R **F** R K	Englehard *et al.*, 1993; Rammensee *et al.*, 1999
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)			23 5 C **K K** **L** **R** PR L	Hill *et al.*, 1992; Sutton *et al.*, 1993; DiBrino *et al.*, 1994b
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
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
B13	RT	333–341	GQGQWTYQI	Honeyborne *et al.*, 2007
B13	Nef	106–114	RQDILDLWI	Harrer *et al.*, 2005
B13	Nef	106–114	RQDILDLWV	Honeyborne *et al.*, 2007

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

HLA	Protein	AA	Sequence	Reference
B14	p2p7p1p6	42–50	CRAPRKKGC	Yu *et al.*, 2002b
B*1401 (B14)	RT	142–149	IRYQYNVL	Rathod, 2006
B*1402 (B14)			23 5 C	DiBrino *et al.*, 1994a
			R R L	
			K H	
			L	
			Y	
			F	
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)			2 C	
			Q Y	Barber *et al.*, 1997
			L F	Barber *et al.*, 1997
			M	Barber *et al.*, 1997
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)			2 9	Barber *et al.*, 1997; Seeger *et al.*, 1998
			T Y	
			S I	
			V	
			F	
B*1516 (B63)	gp160	375–383	SFNCGGEFF	Wilson *et al.*, 1997; Wilson, 1999

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

HLA	Protein	AA	Sequence	Reference
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
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)			12 C **R** **L** **F** K K R R G I A	Jardetzky *et al.*, 1991; Rammensee *et al.*, 1995
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)			2 C **P** **Y** A F V M S L I	Hill *et al.*, 1992; Rammensee *et al.*, 1999
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)	p24	122–130	NPVPVGNIY	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	NPDIVIYQY	Sipsas *et al.*, 1997; Shiga *et al.*, 1996
B*3501 (B35)	RT	175–183	HPDIVIYQY	Rowland-Jones *et al.*, 1995
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

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

HLA	Protein	AA	Sequence	Reference
B*3701 (B37)			2 C **D F** **E M** **L** **I**	Falk *et al.*, 1993
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)			2 C **R L** **H**	Falk *et al.*, 1995a
B*3901 (B39)	p24	61–69	GHQAAMQML	Kurane & West, 1999
B*3910 (B39)	p24	48–56	TPQDLNTML	Honeyborne & Kiepiela, 2005
B*4001 (B60)			2 C **E L**	Falk *et al.*, 1995b
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, 2004
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, 2004
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
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.*, 1997b
B*4402 (B44)			2 C **E F** **Y**	Rammensee *et al.*, 1999
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.*, 1997a

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

HLA	Protein	AA	Sequence	Reference
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, 2004
B51	Vif	57–66	IPLGDAKLII	Bansal *et al.*, 2004
B51	Vpr	29–37	EAVRHFPRI	Cao *et al.*, 2003
B*5101 (B51)			2 C **A F** **P I** **G**	Falk *et al.*, 1995a
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)			2 C **P L**	Hill *et al.*, 1992
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)			2 C **P** A	Barber *et al.*, 1995
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 & 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

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

HLA	Protein	AA	Sequence	Reference
B*5701 (B57)			12 C **A F** **T W** **S** K Y	Barber *et al.*, 1997
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	108–118	TSTLQEQIGWF	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)			12 C **A F** **T W** **S** K V I	Barber *et al.*, 1997; Falk *et al.*, 1995b
B*5801 (B58)	p24	108–117	TSTVEEQQIW	Bertoletti *et al.*, 1998
B*5801 (B58)	p24	108–117	TSTLQEQIGW	Goulder *et al.*, 1996b
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.).

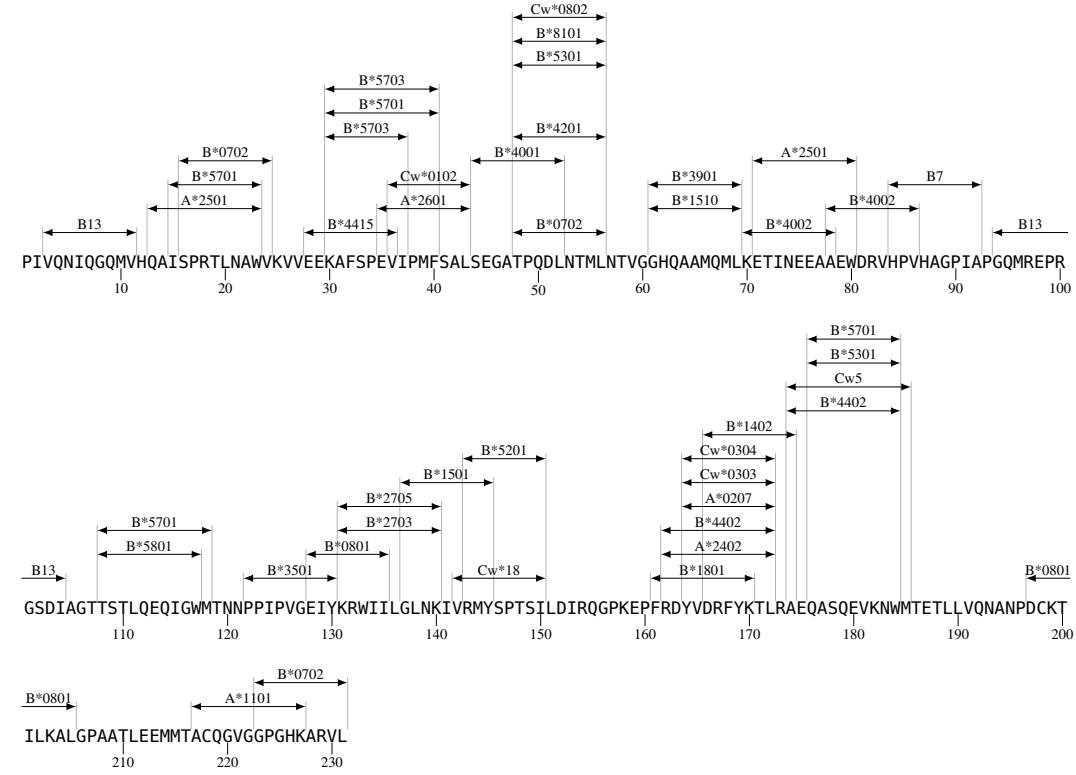
HLA	Protein	AA	Sequence	Reference
Cw*0102 (Cw1)			2 3 C **A L** **L** P	Barber *et al.*, 1997
Cw*0102 (Cw1)	p24	36–43	VIPMFSAL	Goulder *et al.*, 1997a
Cw*0102 (Cw1)	Gag-Pol TF	24–31	NSPTRREL	Liu *et al.*, 2006
Cw3	Nef	83–91	AALDLSHFL	Draenert, 2004
Cw*0303 (Cw9)	p24	164–172	YVDRFFKTL	Honeyborne, 2003
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)			2 6 C **Y L** **P F** **F M** V I L	Falk *et al.*, 1994
Cw*0401 (Cw4)	gp160	375–383	SFNCGGEFF	Wilson *et al.*, 1997; Johnson *et al.*, 1993
Cw5	p24	174–185	AEQASQEVKNWM	Draenert, 2004
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
Cw7	Nef	105–115	RRQDILDLWIY	Yu *et al.*, 2002a
Cw8	gp160	557–565	RAIEAQQHM	Bishop & Honeyborne, 2006
Cw8	Nef	82–91	KAAVDLSHFL	Harrer *et al.*, 1996c
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
Cw*0802 (Cw8)	Nef	83–91	GAFDLSFFL	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-5 Map of optimal HIV-1 CTL epitopes

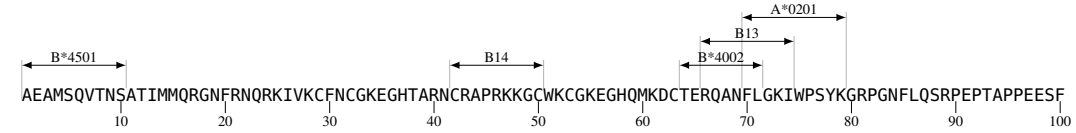
The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence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

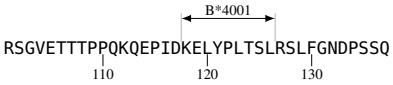
p17 Optimal CTL Epitope Map

p24 Optimal CTL Epitope Map

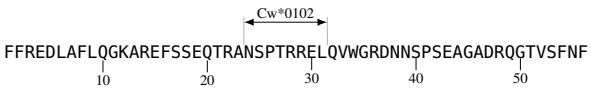


p2p7p1p6 Optimal CTL Epitope Map

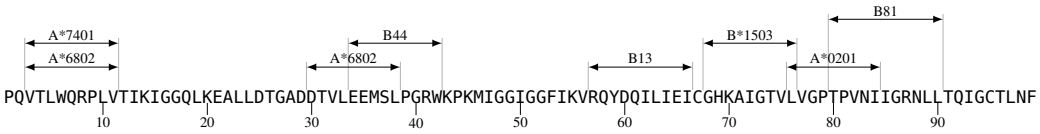




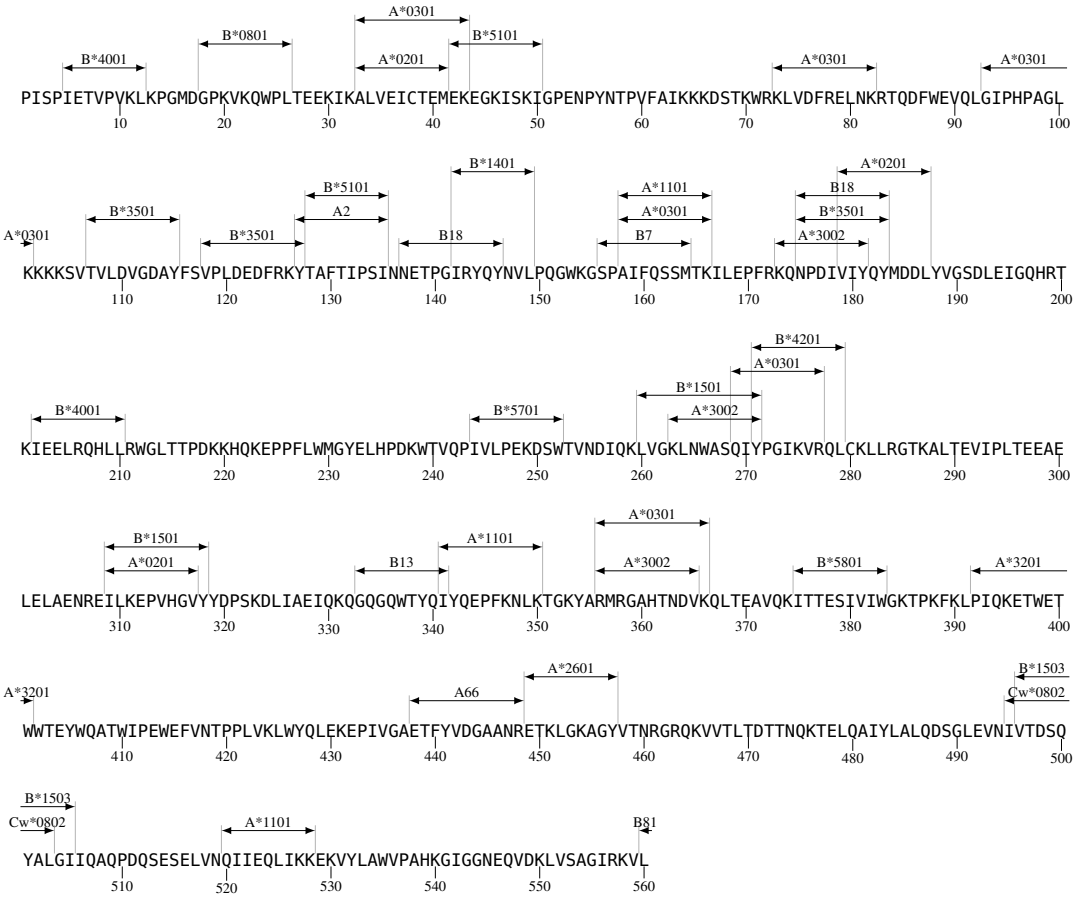
Gag/Pol TF Optimal CTL Epitope Map



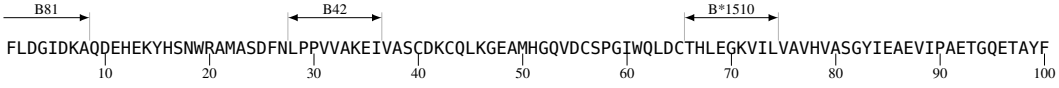
Protease Optimal CTL Epitope Map

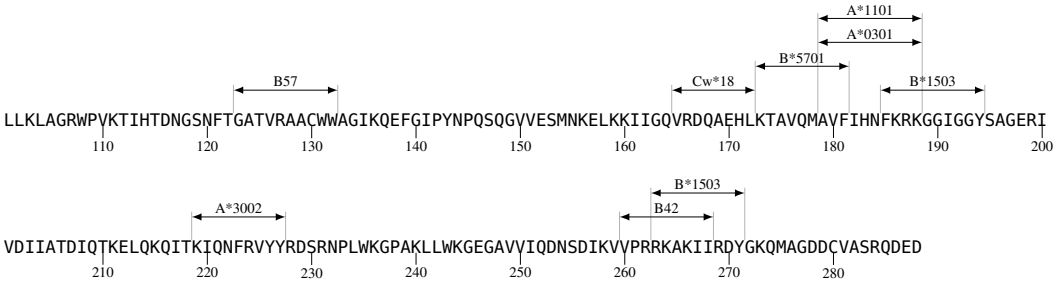


RT Optimal CTL Epitope Map

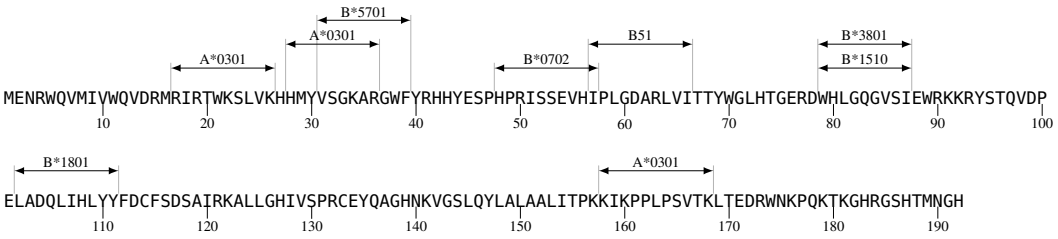


Integrase Optimal CTL Epitope Map

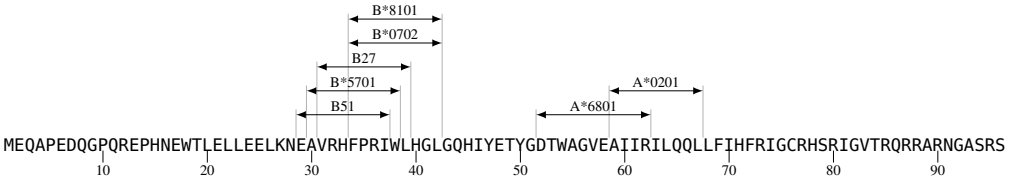




Vif Optimal CTL Epitope Map

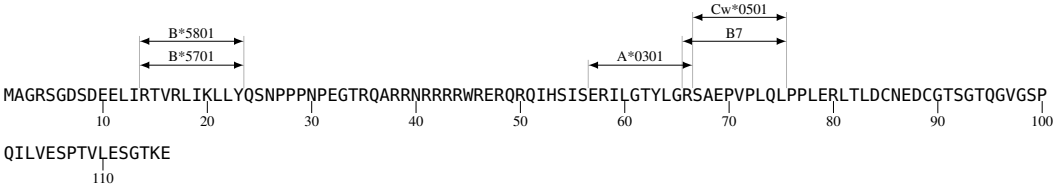


Vpr Optimal CTL Epitope Map



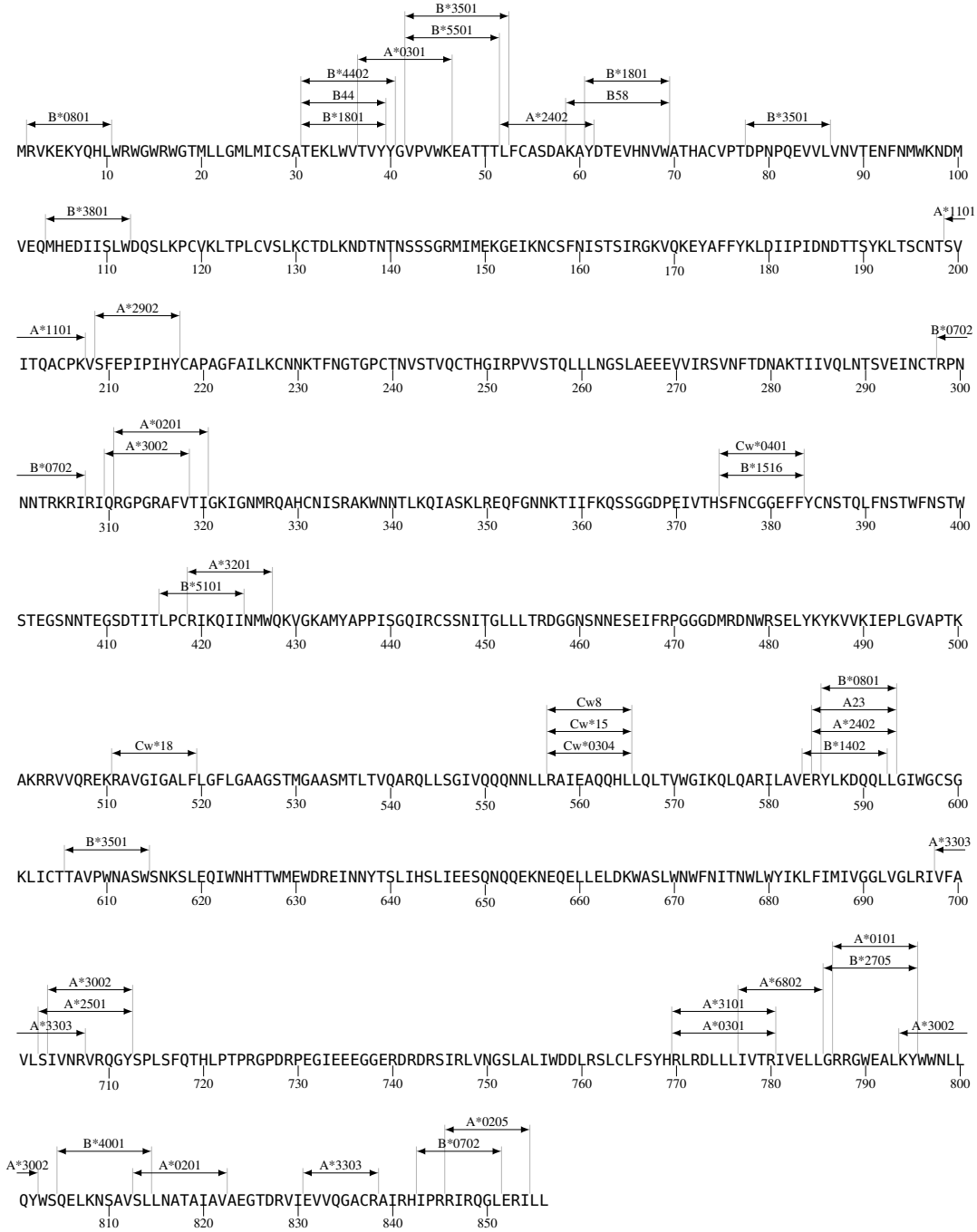
Tat Optimal CTL Epitope Map

Rev Optimal CTL Epitope Map

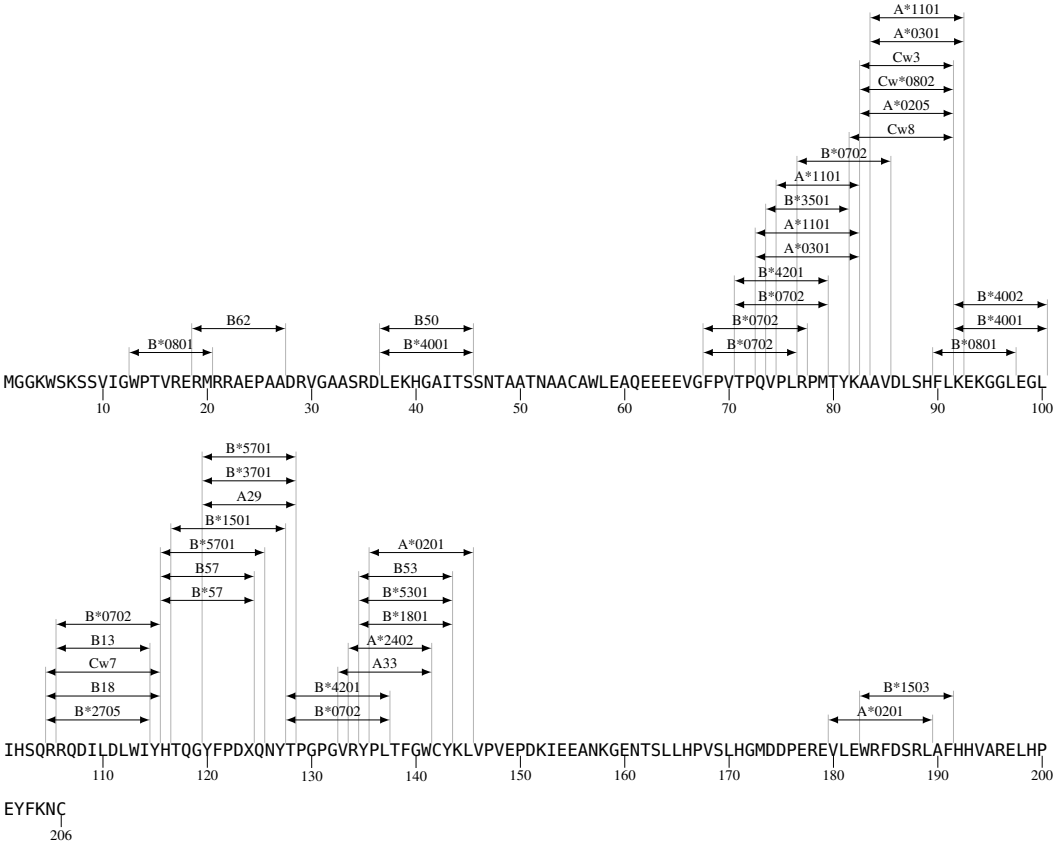


Vpu Optimal CTL Epitope Map

gp160 Optimal CTL Epitope Map



Nef Optimal CTL Epitope Map



I-A-6 Acknowledgments

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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. Please write or call us with any comments you may have.

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