

I-A

Broad HIV-1 Specific CTL Responses Reveal Extensive HLA Class I Binding Promiscuity of HIV-Derived, Optimally Defined CTL Epitopes

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I-A-1 Cytotoxic T lymphocyte (CTL) in HIV infection

Together with neutralizing antibodies and virus specific T-helper cells, HIV specific cytotoxic T lymphocytes (CTL) remain at the center of many vaccine development efforts despite the ongoing debate regarding their *in vivo* induction and function and their potential ability to provide effective protection from infection in vaccines. However, numerous reports support the important role that virus specific CTL responses may have in HIV infection and that their detailed characterization needs to continue. As in past years, we again have compiled an updated list of all optimal HIV derived CTL epitopes that have been described over the last 12 months. The total number of optimal CTL epitopes has now exceeded 200 and increasingly also includes epitopes identified in non-clade B infection and in individuals of non-Caucasian descent. Thus, the collective information on the specificity of these HIV directed responses is of growing relevance for vaccine development in populations most affected by the HIV epidemic and should facilitate further immune analyses in these mostly non-Caucasians ethnicities.

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I-A-2 Broad CTL responses are not associated with HIV control

A number of laboratories, including ours, have in the past described the results from comprehensive CTL screening studies, in which overlapping peptide sets spanning the entire HIV genome are used in IFN- γ ELISpot assays [Addo2003, Cao2003a, Draenert2004d, Feeney2003, Frahm2004, Novitsky2002, Sabbaj2003, Kiepiela2004]. While several reports show either a positive or a negative correlation between viral loads and the breadth or magnitude of these CTL responses, none of these recent studies have found any strong significant associations. Importantly, studies describing correlations have often been based on the analysis of CTL responses against a restricted number of proteins or even single epitopes using tetramer stainings and were often restricted to a relatively low number of subjects enrolled [Betts2001, Buseyne2002a, Buseyne2002b, Edwards2002, Ogg1998]. The larger, more comprehensive studies including individuals at different stages of disease fail to see associations between CTL activity and viral loads [Addo2003, Cao2003a, Draenert2004d, Feeney2003, Frahm2004]. Thus, it appears that either total CTL responses are not a correlate of immune protection, or the assays most widely applied do not reflect the number of CTL responses that actually do mediate effective *in vivo* control of viral replication. The latter may indeed play an important role as some of the most widely used approaches clearly have their limitations. Overcoming them may help to obtain a more accurate picture of the HIV specific CTL activity. For instance, recent studies from our laboratory show that the use of autologous test sequences yields more and stronger CTL responses to variable proteins compared to the use of consensus sequence based peptide sets [Altfeld2003]. Thus, most studies may underestimate the true breadth of responses and may hide a

potential association between CTL activity, viral loads and disease progression. This limitation could be overcome by testing an extensive number of individuals using autologous test sequences; an undertaking that, however, will be limited by the exuberant costs for autologous sequence peptide synthesis.

A further concern regards the use of overlapping peptide panels that span the entire expressed HIV genome. In most cases, these utilize peptides that are 15–18 amino acids in length and which overlap by either 10 or 11 amino acids. Recent studies by Draenert [Draenert2004b] indicate that the precise location of the optimal epitope within the overlapping peptide (OLP) significantly affects recognition of the OLP: if the epitope is located precisely at the C-terminal end of the OLP, it will be significantly better recognized than if located in the middle of the OLP. Recent studies in the SIV macaque model, where peptides can be synthesized that correspond exactly to the autologous virus sequence, indicate that even 15-mers overlapping by 11 amino acids fail to pick up a substantial proportion of the responses (Watkins *et al.*, unpublished). The ultimate and ideal situation would be to use a panel of 11-mers overlapping by 10 amino acids, based on autologous virus sequence. The cost of such an enterprise is prohibitive, but for a limited number of subjects this exercise should perhaps be undertaken, as one becomes increasingly aware of the fact that the immunodominant CTL responses may not necessarily be the ones that are critical for immune control.

In addition, only a few different assays are currently being employed for the detection of virus specific CTL. To our knowledge, all optimal CTL epitopes listed in the present database have been identified either by assessing cytotoxic activity in a Cr⁵¹ release assay or by the induction of IFN- γ in Elispot or intracellular cytokine staining (ICS) assays. While cytolytic function may be an important aspect of effective CTL, IFN- γ release may well be a surrogate for other functions but not occur in all HIV-specific cells. A number of laboratories have tackled these problems and established other assays, such as CD107 degranulation and perforin/granzyme release assays as alternative ways to assess CTL responses. Also, replication inhibition assays of the type first described by Yang *et al.* [Yang1997], in which CTL clones are co-cultured with HLA-matched CD4+ T cells infected with autologous virus clones, may provide a means to come closer to the situation *in vivo*. Such assays will help to address qualitative differences in the viral replication inhibition efficacy of CTL of different specificity and will also help to identify processing mutations that are hard to detect in other, non-replication based assays. The frequency of processing escape mutations is unknown but a recent number of descriptions of mutational processing escape mutations in HIV suggests that this is a mechanism of escape that has been much under-recognized [Draenert2004c, Allen2004, Yokomaku2004]. Overall, these assays still need further adaptation and simplification until comprehensive re-

sponses can be measured on a single peptide level in a larger population of HIV infected individuals.

Finally, assessing total CTL responses by comprehensive screening may detect too many immunologically irrelevant responses and thus obscure a possible association between CTL activity and viral control. Indeed, there is compelling evidence that some single epitope-specific responses can control viral replication as viral escape in such epitopes is associated with increased viral loads and acceleration of disease progression [Draenert2004c, Goulder1997c, Cao2003b, Kelleher2001, Allen2000, Barouch2002, Klenerman2002, Leslie2004, Friedrich2004]. Thus, besides single responses that appear to have the capacity to provide strong immune surveillance, the current assays may also detect many less efficient responses and thus hide a possible association between CTL activity and viral load. On the other hand, individuals with high viral loads and fast disease progression can well maintain strong CTL responses without evidence of affecting viral replication [Draenert2004d]. In this study, the lack of control over viral replication could not be explained by sequence variation in the targeted regions of the autologous virus, indicating functional deficiencies specific to these individuals or responses. New data from our lab and other investigators suggest that the ability of HIV-epitope specific CTL to proliferate in response to antigen is lost in the course of infection, and that this defect could be associated with the loss of effective control over viral replication [Migueles2002] (and Lichtenfeld *et al.*, unpublished). Together, these studies suggest that at least some HIV specific CTL can exert effective replication control and that the often generalized description of “functional deficiency of HIV specific CTL” is likely an over-simplification.

I-A-3 Extensive HLA class I binding promiscuity of HIV derived optimal epitopes

Regardless of possible associations between CTL activity and viral loads, knowing the precise targets of these CTL is still a prerequisite for many other questions to be asked, such as viral evolution, genetic imprinting and their potential use in epitope-based vaccines. Furthermore, the well-defined epitope landscape can be used to address questions of antigen processing and epitope presentation. In a recent study, we have used the optimally defined CTL epitopes to address the degree of HLA class I binding promiscuity. Briefly, 100 HIV infected individuals of mainly non-Caucasian background were tested for CTL responses against almost 200 described, optimal HIV derived CTL epitopes, regardless of the individual's HLA type. Interestingly, only about 40% of all responses were

detected in individuals who expressed the appropriate HLA class I allele. Another 20% of the responses were attributed to the presence of an allele that fell into the same HLA-supertype as the originally described restricting allele (for instance, an HLA-A3+ individual showing a positive response against an HLA-A11 restricted epitope). This left 40% of all responses to be restricted by alleles that do not share obvious similarities to the originally described allele or were, thus far at least, not grouped into the same HLA-supertype as the original allele. Although more detailed analyses will be required to confirm the precise length and anchor residues for the epitopes presented on alternative alleles, the data strongly suggest the presence of epitopes with wide HLA-class I binding promiscuity. This is supported by some of the epitopes included in the present update, for which presentation and *ex vivo* recognition was documented for up to four different HLA class I alleles (TL9 on B7, B42, B81 and Cw08). Furthermore, strong support for extensive epitope binding promiscuity is derived from the observation that CTL responses to certain regions of the viral genome, such as Gag and Nef, show strong clustering of responses [Frahm2004, Frahm2002a]. In data now publicly available at the Los Alamos database (<http://www.hiv.lanl.gov/content/immunology/hlatem/>), we show that 72 of 150 individuals tested reacted to the very same overlapping 18-mer peptide in Nef. Since these individuals expressed widely diverse HLA types and the number of potential epitopes in a single 18-mer is limited, the data strongly suggest that at least some epitopes must be presented by multiple HLA class I alleles.

I-A-4 Implications for vaccine development and viral evolution studies

Clearly, the identification of CTL epitopes that can bind multiple HLA class I alleles will facilitate the selection of epitopes with an increased population coverage. However, it will also be important to assess potential functional differences between responses to the same epitopes presented on different alleles. This may be of special interest in cases where the epitopes are shared between HLA class I alleles differentially associated with slow or fast HIV disease progression. An example of this is the TL9 response restricted by HLA-B42 and B81. HLA-B81 is associated with low viral loads in the Durban population, whereas B42 is not (Goulder *et al.*, unpublished). Sequencing of the virus indicates that escape mutations are selected in the B81-positive subjects in the region of the virus encoding the TL9 epitope, whereas this does not occur in the B42-positive subjects (Leslie *et al.*, unpublished). Other examples include the epitope QW9, shared by HLA-B57 (slow) and HLA-B53 (fast disease progression). Using these epitopes,

one may be able to address the role that the HLA class I molecule or the presented CTL epitope, respectively, play in determining the rate of disease progression. Finally, cross-binding epitopes may also impact the analyses of CTL escape patterns as allele-associated footprints may need to take into consideration other alleles with the ability to share CTL epitopes. Similarly, the assessment of a “functional HLA homozygosity” in which alleles that frequently share CTL epitopes are considered “functionally homozygous” may reveal additional insight into the mechanism by which genetically homozygous individuals show a faster disease progression compared to HLA heterozygous subjects [Carrington1999].

I-A-5 Acknowledgments

As every year, we would like to express our gratitude to the large number of researchers in the field who continuously contribute to this database. The mostly unpublished data added to this years update stemming from the AIDS Research Center at Mass. General Hospital have been largely funded by an NIH contract (#NO1-A1-15442) supporting HLA typing and HIV CTL epitope definition in non-Caucasian populations and non clade B HIV infection.

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 at:

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I-A-6 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	Cao2002
A*02 (A2)	RT	127–135	YTAFTIPSV	Draenert2004a
A*0201 (A2)			2 6 C 1° anchor L L M V 2° anchor V	Falk1991, Barouch1995
A*0201 (A2)	p17	77–85	SLYNTVATL	Johnson1991, Parker1992, Parker1994
A*0201 (A2)	p1	1–10	FLGKIWPSYK	Yu2002b
A*0201 (A2)	RT	33–41	ALVEICTEM	Haas1998, Haas1999
A*0201 (A2)	RT	179–187	VIYQYMDDL	Harrer1996a
A*0201 (A2)	RT	309–317	ILKEPVHGV	Walker1989, Tsomides1991
A*0201 (A2)	Vpr	59–67	AIIRILQQL	Altfeld2001a, Altfeld2001b
A*0201 (A2)	gp160	311–320	RGPGRAFVTI	Alexander-Miller1996
A*0201 (A2)	gp160	813–822	SLLNATDIAV	Dupuis1995
A*0201 (A2)	Nef	136–145	PLTFGWCYKL	Haas1996, Maier1999
A*0201 (A2)	Nef	180–189	VLEWRFD SRL	Haas1996, Maier1999
A*0202 (A2)			2 C L L V	Barouch1995
A*0202 (A2)	p17	77–85	SLYNTVATL	Goulder1999
A*0205 (A2)	p17	77–85	SLYNTVATL	Goulder1999
A*0205 (A2)	gp41	335–343	RIRQGLERA	Sabbaj2003
A*0207 (A2)	p24	164–172	YVDRFYKTL	Currier2002

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

HLA	Protein	AA	Sequence	Reference
A*0301 (A3)	p17	18–26	KIRLRPGGK	Harrer1996b
A*0301 (A3)	p17	20–28	RLRPGGKKK	Goulder1997b, Culmann1999, Lewinsohn1999b, Wilkes1999b
A*0301 (A3)	p17	20–29	RLRPGGKKKY	Goulder2000b
A*0301 (A3)	RT	33–43	ALVEICTEMEK	Haas1998, Haas1999
A*0301 (A3)	RT	73–82	KLVDVFRELNK	Yu2002a
A*0301 (A3)	RT	93–101	GIPHPAGLK	Yu2002a
A*0301 (A3)	RT	158–166	AIFQSSMTK	Threlkeld1997
A*0301 (A3)	RT	269–277	QIYPGIKVR	Yu2002a
A*0301 (A3)	RT	356–366	RMRGAHTNDVK	Yu2002a
A*0301 (A3)	Integrase	179–188	AVFIHNFKRK	Yu2002a
A*0301 (A3)	Vif	17–26	RIRTWKSLVK	Altfeld2001a, Yu2002a
A*0301 (A3)	Vif	28–36	HMYISKKAK	Yu2002a
A*0301 (A3)	Vif	158–168	KTKPPLPSVKK	Yu2002a
A*0301 (A3)	Rev	57–66	ERILSTYLGR	Addo2002a, Yu2002a
A*0301 (A3)	gp160	37–46	TVYYGVPVWK	Johnson1994a
A*0301 (A3)	gp160	770–780	RLRDLLLIVTR	Takahashi1991
A*0301 (A3)	Nef	73–82	QVPLRPMTYK	Koenig1990, Culmann1991
A*0301 (A3)	Nef	84–92	AVDLSHFLK	Yu2002a
A*1101 (A11)			2 C K V I F Y	Zhang1993, Rammensee1995
A*1101 (A11)	p17	84–92	TLYCVHQRI	Harrer1998
A*1101 (A11)	p24	217–227	ACQGVGGPGHK	Sipsas1997
A*1101 (A11)	RT	158–166	AIFQSSMTK	Johnson1994b, Zhang1993, Threlkeld1997
A*1101 (A11)	RT	341–350	IYQEPFKNLK	Culmann1999
A*1101 (A11)	RNase	80–88	QIIEQLIKK	Fukada1999
A*1101 (A11)	Integrase	179–188	AVFIHNFKRK	Fukada1999
A*1101 (A11)	gp160	199–207	SVITQACPK	Fukada1999
A*1101 (A11)	Nef	73–82	QVPLRPMTYK	Buseyne1999
A*1101 (A11)	Nef	75–82	PLRPMTYK	Culmann1991
A*1101 (A11)	Nef	84–92	AVDLSHFLK	Culmann1991

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

HLA	Protein	AA	Sequence	Reference
A*23 (A23)	gp41	74–82	RYLKDQQLL	Cao2003a
A*2402 (A24)			2 C Y I L F	Maier1994
A*2402 (A24)	p17	28–36	KYKLVHIVW	Ikeda-Moore1998, Lewinsohn1999a
A*2402 (A24)	p24	162–172	RDYVDRFFKTL	Dorrell1999, Rowland-Jones1999
A*2402 (A24)	gp160	52–61	LFCASDAKAY	Lieberman1992, Shankar1996
A*2402 (A24)	gp160	585–593	RYLKDQQLL	Dai1992
A*2402 (A24)	Nef	134–141	RYPLTFGW	Goulder1997a, Ikeda-Moore1998
A*2501 (A25)	p24	13–23	QAISPRTLNAW	Kurane1999
A*2501 (A25)	p24	71–80	ETINEEAAEW	Klenerman1996, vanBaalen1996
A*2601 (A26)			12 6 C V Y T F I L F D I E L V	Dumrese1998
A*2601 (A26)	p24	35–43	EVIPMFSAL	Goulder1996a
A*2601 (A26)	Pol	604–612	ETKLGKAGY	Sabbaj2003
A*29 (A29)	Nef	120–128	YFPDWQNYT	Draenert2004b
A*2902 (A29)	gp160	209–217	SFEPIPIHY	Altfeld2000a

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

HLA	Protein	AA	Sequence	Reference
A*3002 (A30)			12 Y F L V R	C Y Rammensee1999
A*3002 (A30)	p17	76–86	RSLYNTVATLY	Goulder2001
A*3002 (A30)	RT	173–181	KQNPDIIVY	Goulder2001
A*3002 (A30)	RT	263–271	KLNWASQIY	Goulder2001
A*3002 (A30)	RT	356–365	RMRGAHTNDV	Sabbaj2003
A*3002 (A30)	Integrase	219–227	KIQNFRVYY	Sabbaj2003, Rodriguez2004
A*3002 (A30)	gp160	704–712	IVNRNRQGY	Goulder2001
A*3002 (A30)	gp120	310–318	HIGPGRAFY	Sabbaj2003
A*3002 (A30)	gp41	283–291	KYCWNLLQY	Goulder2001
A*3101 (A31)			2 L V Y F	C R Falk1994, Rammensee1999
A*3101 (A31)	gp160	770–780	RLRDLILLIVTR	Safrit1994a, Safrit1994b
A*3201 (A32)	RT	392–401	PIQKETWETW	Harrer1996b
A*3201 (A32)	gp160	419–427	RIKQIINMW	Harrer1996b
A*3303 (A33)	gp41	187–196	VFAVLSIVNR	Hossain2001
A*3303 (A33)	gp41	320–327	EVAQRAYR	Hossain2001
A*3303 (A33)	Vpu	29–37	EYRKILRQR	Addo2002b
A*3303 (A33)	Nef	133–141	TRYPLTFGW	Cao2002
A*6801 (A68)	Tat	39–49	ITKGLGISYGR	Oxenius2002
A*6801 (A68)	Vpr	52–62	DTWAGVEAIR	Sabbaj2004
A*6802 (A68)	Protease	3–11	ITLWQRPLV	Rowland-Jones1999
A*6802 (A68)	Protease	30–38	DTVLEEWNL	Rowland-Jones1999
A*6802 (A68)	gp160	777–785	IVTRIVELL	Wilkes1999a
A*7401 (A19)	Protease	3–11	ITLWQRPLV	Rowland-Jones1999

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

HLA	Protein	AA	Sequence	Reference
B*07 (B7)	p24	84–92	HPVHAGPIA	Yu2002a
B*0702 (B7)			123 C P L A R F R K	Englehard1993, Rammensee1999
B*0702 (B7)	p24	16–24	SPRTLNAWV	Lewinsohn1999a
B*0702 (B7)	p24	48–56	TPQDLNTML	Wilson1999a, Wilkes1999c, Jin2000, Wilson1997
B*0702 (B7)	p24	223–231	GPGHKARVL	Goulder1999
B*0702 (B7)	Vpr	34–42	FPRIWLHGL	Altfeld2001a
B*0702 (B7)	Vif	48–57	HPRVSSEVHI	Altfeld2001a
B*0702 (B7)	gp160	298–307	RPNNNTRKSI	Safrit1994b
B*0702 (B7)	gp160	843–851	IPRRIRQGL	Wilkes1999b
B*0702 (B7)	Nef	68–77	FPVTPQVPLR	Haas1996, Maier1999
B*0702 (B7)	Nef	68–76	FPVTPQVPL	Bauer1997, Frahm2002b
B*0702 (B7)	Nef	71–79	TPQVPLRPM	Goulder1999
B*0702 (B7)	Nef	77–85	RPMTYKAAL	Bauer1997
B*0702 (B7)	Nef	106–115	RQDILDLDWIY	Goulder1999
B*0702 (B7)	Nef	128–137	TPGPGVRYPL	Culmann-Penciolelli1994, Haas1996
B*0801 (B8)			23 5 C K K L R PR L	Hill1992, Sutton1993, DiBrino1994b
B*0801 (B8)	p17	24–32	GGKKKYKLLK	Rowland-Jones1993, Goulder1997d
B*0801 (B8)	p17	74–82	ELRSLYNTV	Goulder1997d
B*0801 (B8)	p24	128–135	EIYKRWII	Sutton1993, Goulder1997d
B*0801 (B8)	p24	197–205	DCKTILKAL	Sutton1993
B*0801 (B8)	RT	18–26	GPKVKQWPL	Walker1989, Sutton1993
B*0801 (B8)	gp160	2–10	RVKEKYQHL	Sipsas1997
B*0801 (B8)	gp160	586–593	YLKDQQLL	Johnson1992, Shankar1996
B*0801 (B8)	Nef	13–20	WPTVRERM	Goulder1997d
B*0801 (B8)	Nef	90–97	FLKEKGGL	Culmann-Penciolelli1994, Price1997

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

HLA	Protein	AA	Sequence	Reference
B*14 (B14)	p15	42–50	CRAPRKKGC	Yu2002b
B*1402 (B14)			23 5 C R R L K H L Y F	DiBrino1994a
B*1402 (B14)	p24	166–174	DRFYKTLRA	Harrer1996b
B*1402 (B14)	gp160	584–592	ERYLKDQQL	Johnson1992
B*1501 (B62)			2 C Q Y L F M	Barber1997 Barber1997 Barber1997
B*1501 (B62)	p24	137–145	GLNKIVRMV	Johnson1991, Goulder1999
B*1501 (B62)	RT	260–271	LVGKLNWASQIY	Johnson1999
B*1501 (B62)	RT	309–318	ILKEPVHGVY	Johnson1991, Johnson1999
B*1501 (B62)	Nef	19–27	RMRRAEPAA	Cao2002
B*1501 (B62)	Nef	117–127	TQGYFPDWQNY	Culmann1999
B*1503 (B72)	Integrase	185–194	FKRKGGIGGY	Honeyborne2003
B*1503 (B72)	Integrase	263–271	RKAKIIRDY	Cao2003a
B*1503 (B72)	Tat	38–47	FQTKGLGISY	Novitsky2001
B*1503 (B72)	Pol	651–660	VTDSQYALGI	Sabbaj2003
B*1503 (B72)	Nef	183–191	WRFDSRLAF	Cao2002
B*1510 (B71)	Gag p24	61–69	GHQAAMQML	Day2003
B*1510 (B71)	Vif	79–87	WHLGHVSI	Honeyborne2003
B*1516 (B63)			2 9 T Y S I V F	Barber1997, Seeger1998
B*1516 (B63)	gp160	375–383	SFNCGGEFF	Wilson1997, Wilson1999a

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

HLA	Protein	AA	Sequence	Reference
B*1801 (B18)	p24	161–170	FRDYVDRFYK	Ogg1998
B*1801 (B18)	Vif	102–111	LADQLIHLHY	Altfeld2001a
B*1801 (B18)	Nef	135–143	YPLTFGWCY	Culmann1991, Culmann-Penciolelli1994
B*27 (B27)	Vpr	31–39	VRHFPRWL	Addo2004
B*2703 (B27)	p24	131–140	RRWIQLGLQK	Rowland-Jones1998, Rowland-Jones1999
B*2705 (B27)			12 C R L F K K R R G I A	Jardetzky1991, Rammensee1995
B*2705 (B27)	p17	19–27	IRLRPGGKK	McKinney1999, Lewinsohn1999a
B*2705 (B27)	p24	131–140	KRWIILGLNK	Nixon1988, Buseyne1993, Goulder1997c
B*2705 (B27)	gp160	786–795	GRRGWKALY	Lieberman1992, Lieberman1999
B*2705 (B27)	Nef	105–114	RRQDILDLWI	Goulder1997b
B*3501 (B35)			2 C P Y A F V M S L I	Hill1992, Rammensee1999
B*3501 (B35)	p17	36–44	WASRELERF	Goulder1997a
B*3501 (B35)	p17	124–132	NSSKVSQNY	Rowland-Jones1995
B*3501 (B35)	p24	122–130	PPIPVGDIY	Rowland-Jones1995
B*3501 (B35)	p24	122–130	NPVPVGNLY	Rowland-Jones1995
B*3501 (B35)	RT	107–115	TVLDVGDAY	Wilkes1999b, Wilson1999b
B*3501 (B35)	RT	118–127	VPLDEDFRKY	Sipsas1997, Shiga1996
B*3501 (B35)	RT	175–183	NPDIVLYQY	Sipsas1997, Shiga1996
B*3501 (B35)	RT	175–183	HPDIVLYQY	Rowland-Jones1995
B*3501 (B35)	gp160	42–52	VPVWKEATTTL	Wilkes1999b
B*3501 (B35)	gp160	78–86	DPNPQEVVL	Shiga1996
B*3501 (B35)	gp160	606–614	TAVPWNASW	Johnson1994a
B*3501 (B35)	Nef	74–81	VPLRPMTY	Culmann1991, Culmann-Penciolelli1994

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

HLA	Protein	AA	Sequence	Reference	
B*3701 (B37)			2 C	Falk1993	
			D F		
			E M		
			L		
			I		
B*3701 (B37)	Nef	120–128	YFPDWQNYT	Culmann1991, Culmann1999	
B*3801 (B38)	Vif	79–87	WHLGQGVSI	Sabbaj2004	
B*3801 (B38)	gp160	104–112	MHEDIISLW	Cao2002	
B*3901 (B39)			2 C	Falk1995a	
			R L		
			H		
B*3901 (B39)	p24	61–69	GHQAAMQML	Kurane1999	
B*4001 (B60)			2 C	Falk1995b	
			E L		
	B*4001 (B60)	p17	92–101	IEIKDTKEAL	Altfeld2000b
	B*4001 (B60)	p24	44–52	SEGATPQDL	Altfeld2000b
	B*4001 (B60)	p6	33–41	KELYPLTSL	Yu2002b
	B*4001 (B60)	RT	5–12	IETVPVKL	Draenert2004a
	B*4001 (B60)	RT	202–210	IEELRQHLL	Altfeld2000b
	B*4001 (B60)	gp160	805–814	QELKNSAVSL	Altfeld2000b
	B*4001 (B60)	Nef	37–45	LEKHGAITS	Draenert2004a
	B*4001 (B60)	Nef	92–100	KEKGGLEGL	Altfeld2000b
	B*4002 (B61)	p17	11–19	GELDRWEKI	Sabbaj2003
B*4002 (B61)	p24	70–78	KETINEEAA	Sabbaj2003	
B*4002 (B61)	p24	78–86	AEWDRVHPV	Sabbaj2003	
B*4002 (B61)	p15	64–71	TERQANFL	Sabbaj2003	
B*4002 (B61)	Nef	92–100	KEKGGLEGL	Sabbaj2003, Altfeld2000b	
B*42 (B42)	Integrase	260–268	VPRRKAKII	Kiepiela2002	
B*4201 (B42)	p24	48–56	TPQDLNTML	Goulder2000a	
B*4201 (B42)	RT	271–279	YPGIKVRQL	Wilkes1999b	
B*4201 (B42)	Nef	128–137	TPGPGVRYPL	Goulder1999	

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

HLA	Protein	AA	Sequence	Reference
B*44 (B44)	Protease	34–42	EEMNLPGRW	Rodriguez2004
B*4402 (B44)			2 C E F Y	Rammensee1999
B*4402 (B44)	p24	162–172	RDYVDRFYKTL	Ogg1998
B*4402 (B44)	p24	174–184	AEQASQDVKNW	Lewinsohn1999a
B*4402 (B44)	gp160	31–40	AENLWVTVYY	Borrow1997
B*4415 (B12)	p24	28–36	EEKAFSPEV	Bird2002
B*4501 (B45)	Gag-p2	1–10	AEAMSQVTNS	Sabbaj2004
B*50 (B50)	Nef	37–45	LEKHGAITS	Draenert2004a
B*51 (B51)	Vif	57–66	IPLGDAKLII	Bansal2004
B*51 (B51)	Vpr	29–37	EAVRHFPRI	Cao2003a
B*5101 (B51)			2 C A F P I G	Falk1995a
B*5101 (B51)	RT	42–50	EKEGKISKI	Haas1998, Haas1999
B*5101 (B51)	RT	128–135	TAFTIPSI	Sipsas1997
B*5101 (B51)	gp160	416–424	LPCRKIQII	Tomiyama1999
B*5201 (B52)			2 C I V	Rammensee1999
B*5201 (B52)	p24	143–150	Q RMYSPTSI	Wilkes1999b, Wilson1997
B*53 (B53)	Nef	135–143	YPLTFGWCF	Kiepiela2002

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

HLA	Protein	AA	Sequence	Reference
B*5301 (B53)			2 C P L	Hill1992
B*5301 (B53)	p24	48–56	TPYDINQML	Gotch1993
B*5301 (B53)	p24	176–184	QASQEVKNW	Buseyne1996, Buseyne1997, Buseyne1999
B*5301 (B53)	Tat	2–11	EPVDPRLEPW	Addo2001
B*5301 (B53)	Nef	135–143	YPLTFGWCY	Sabbaj2003
B*5501 (B55)			2 C P	Barber1995
			A	
B*5501 (B55)	gp160	42–51	VPVWKEATTT	Shankar1996, Lieberman1999
B*57 (B57)	Integrase	123–132	STTVKAACWW	Rodriguez2004, Addo2004
B*57 (B57)	Nef	116–124	HTQGYFPDW	Draenert2002
B*5701 (B57)			12 C A F T W S	Barber1997
			K Y	
B*5701 (B57)	p24	15–23	ISPRTLNAW	Johnson1991, Goulder1996b
B*5701 (B57)	p24	30–40	KAFSPEVIPMF	Goulder1996b
B*5701 (B57)	p24	108–118	TSTLQEQIGWF	Goulder1996b
B*5701 (B57)	p24	176–184	QASQEVKNW	Goulder1996b
B*5701 (B57)	RT	244–252	IVLPEKDSW	vanderBurg1997, Hay1999
B*5701 (B57)	Integrase	173–181	KTAVQMAVF	Goulder1996b, Hay1999
B*5701 (B57)	Vpr	30–38	AVRHFPRIW	Altfeld2001a
B*5701 (B57)	Vif	31–39	ISKKAKGWF	Altfeld2001a
B*5701 (B57)	Rev	14–23	KAVRLIKFLY	Addo2001
B*5701 (B57)	Nef	116–125	HTQGYFPDWQ	Culmann1991
B*5701 (B57)	Nef	120–128	YFPDWQNYT	Culmann1991
B57 (B57)	Nef	116–124	HTQGYFPDW	Draenert2002
B*5703 (B57)	p24	30–37	KAFSPEVI	Goulder2000b
B*5703 (B57)	p24	30–40	KAFSPEVIPMF	Goulder2000b

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

HLA	Protein	AA	Sequence	Reference
B*5801 (B58)			12 C A F T W S K V I	Barber1997, Falk1995b
B*5801 (B58)	p24	108–117	TSTVEEQQIW	Bertoletti1998
B*5801 (B58)	p24	108–117	TSTLQEQIGW	Goulder1996b
B*5801 (B58)	RT	375–383	IAMESIVIW	Kiepiela2002
B*5801 (B58)	Rev	14–23	KAVRLIKFLY	Addo2001
B*81 (B81)	Pol	715–723	LFLDGIDKA	Addo2002a
B*8101 (B81)	p24	48–56	TPQDLNTML	Goulder2000a
B*8101 (B81)	Vpr	34–42	FPRIWLHGL	Altfeld2001a
Cw*0102 (Cw1)			23 C A L L P	Barber1997
Cw*0102 (Cw1)	p24	36–43	VIPMFSAL	Goulder1997a
Cw*03 (Cw03)	Nef	83–91	AALDLSHFL	Draenert2004a
Cw*0303 (Cw9)	Gag p24	164–172	YVDRFFKTL	Honeyborne2003
Cw*0304 (Cw10)	Gag p24	164–172	YVDRFFKTL	Honeyborne2003
Cw*0304 (Cw10)	gp41	46–54	RAIEAQQHL	Currier2002, Trocha2002
Cw*0401 (Cw4)			2 6 C Y L P F F M V I L	Falk1994
Cw*0401 (Cw4)	gp160	375–383	SFNCGGEFF	Wilson1997, Johnson1993

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

HLA	Protein	AA	Sequence	Reference
Cw*05 (Cw05)	Gag p24	174–185	AEQASQEVKNWM	Draenert2004a
Cw*07 (Cw7)	Nef	105–115	KRQEILDLWVY	Kiepiela2002
Cw*07 (Cw7)	Nef	105–115	RRQDILDLWIY	Yu2002a
Cw*0802 (Cw8)	p24	48–56	TPQDLNTML	Goulder2000a
Cw*0802 (Cw8)	Nef	83–91	AAVDLSHFL	Cao2003a
Cw*12 (Cw12)	Tat	30–37	CCFHCQVC	Cao2003a, Nixon1999
Cw*15 (Cw15)	gp41	46–54	RAIEAQQHL	Trocha2002

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