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TCR clonotypes: molecular determinants of T-cell efficacy against HIV

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Running title: HIV-specific T-cell response and TCR repertoire
Abstract
Due to the enormous complexity and breadth of the overall HIV-specific CD8+ T-cell response, invaluable information regarding important aspects of T-cell efficacy against HIV can be sourced from studies performed on individual clonotypes. Data gathered from *ex-vivo* and *in vitro* analyses of T-cell responses and viral evolution bring us one step closer towards deciphering the correlates of protection against HIV. HIV-responsive CD8+ T-cell populations are characterized by specific clonotypic immunodominance patterns and public TCRs. The TCR endows T-cells with two key features, important for the effective control of HIV: avidity and crossreactivity. While TCR avidity is a major determinant of CD8+ T-cell functional efficacy against the virus, crossreactivity towards wildtype and mutant viral epitopes is crucial for adaptation to HIV evolution. The properties of CD4+ T-cell responses in HIV controllers appear also to be shaped by high avidity public TCR clonotypes. The molecular nature of the TCR, together with the clonotypic composition of the HIV-specific T-cell response, emerge as major determinants of anti-viral efficacy.

Keywords
TCR / T-cells / HIV / efficacy / avidity
Introduction
The central role of T-cell mediated immunity in limiting viral replication has long been established, while the precise determinants of HIV-specific T-cell efficacy have been investigated for over two decades. Early studies of CD8+ and CD4+ T-cell responses against HIV concentrated on the importance of their magnitude, epitope specificity, and antigenic breadth, as well as their differentiation and ‘exhaustion’ phenotypes. Technological advances have facilitated in depth analyses of qualitative or functional T-cell attributes (e.g. proliferative potential, secretion of multiple effector molecules and HIV suppressive capacity). Several of these parameters have been directly associated with a better control of HIV infection, documented in a unique group of controller patients, who are able to maintain undetectable viral replication in the absence of anti-retroviral treatment [1, 2]. However, the vast majority of these studies lacked the mechanistic insights into the basis of HIV control by T-cells, information essential for advancing the development of effective immunotherapeutic strategies against the virus. In recent years, the focus has shifted to the study of HIV-specific T-cell receptor (TCR) signatures or clonotypes, which represent the fundamental units of the T-cell response. Unique TCRs are generated through the rearrangement of genes encoding TCR α and β chains during T-cell maturation. The TCR defines T-cell specificity though the recognition of foreign peptide antigens presented by major histocompatibility complex (MHC) molecules. Additionally, it dictates the strength of binding, or the affinity of the TCR/peptide-MHC (pMHC) interaction, which has a profound bearing on the functional outcome, and consequently, the clearance of infection. We review here the recent findings relating to the study of the HIV-specific TCR repertoire, and how these help us to deconvolute the complexity of the T-cell response against HIV.
**TCR repertoire and CD8+ T-cell immunodominance patterns**

Over the last 20 years, studies of TCR gene usage have yielded key insights into the clonotypic composition of HIV-specific CD8+ T-cell populations. Initial work revealed that a population of CD8+ T-cells responding to a given HIV epitope (i.e. a gp41-derived HLA-B*14 restricted peptide) is composed of multiple clonotypes, associated with a certain level of TCR diversity [3]. Of note, these clonotypes can possess distinct phenotypic attributes, such as differentiation marker or co-inhibitory receptor expression [4, 5]. From this important observation we can infer that TCR repertoire diversity can evoke variable functional outcomes. Minor HIV-derived epitope differences can also impact dramatically on the TCR repertoire of an epitope-specific CD8+ T-cell response against the virus. For instance, the clonotypic characteristics of CD8+ T-cell populations elicited by HIV-1 subtype A or subtype C Gag-TL9 epitopes (which differ at a single amino acid position) were totally distinct [6]. Interestingly, while CD8+ T-cell responses against subtype C TL9 expressed TCRs that used almost exclusively the TRBV12-3 gene, subtype A TL9-specific CD8+ T-cells employed a completely different and more diverse TRBV gene assortment. A recent study has also revealed that superimposed epitopes, in which a shorter epitope is embedded within a longer one, presented by the same HLA class I molecule (i.e. HLA-A*24:02-restricted superimposed HIV Nef epitopes RYPLTFGWCF (RF10) and RYPLTFGW (RW8)), could drive distinct HIV-specific CD8+ T-cell repertoires, exhibiting distinct TCR repertoire composition and properties [7].

While some HIV-specific clonotypes can be stable and persist for several years in patients [8], the overall clonotypic composition of HIV-specific CD8+ T-cell populations is not fixed. Instead, it evolves over time, as shown in studies of HLA-B*08-restricted Nef FLKEKGGL (FL8) or HLA-B*27:05 restricted Gag KRWIILGLNK (KK10)-specific cells [9, 10]. Nonetheless, despite TCR repertoire diversity and flexibility, biased TCR gene usage has also been reported in several HIV-specific CD8+ T-cell populations (e.g. TRBV13.2 in the HLA-B*08-restricted Nef FL8 epitope system and TRBV7 in the HLA B*57-restricted gag KAFSPEVIPMF epitope system), supporting the notion of selective clonotype recruitment during the course of HIV infection [11, 12]. In recent years, an increasing number of studies have even reported the presence of public TCRs, usually defined as amino acid residue-identical TRBV sequences that occur in multiple individuals [13, 14]. Of note, epitope-specific usage of public TCRs has been directly correlated with immunodominance hierarchy across 20 HIV epitopes restricted by HLA-B*42:01 [14]. Public clonotype usage has also identified protective Gag-specific CD8+ T-cell responses in SIV-infected Mamu-A*01+ rhesus macaques [15]. Public clonotypes may be present at higher frequencies in the naive repertoire and
thus be more rapidly amplified upon antigenic stimulation. Alternatively, they might represent optimal "solutions" for the recognition of specific pMHC complexes, thus conferring them the capacity to contain the virus more promptly or effectively. Collectively, these studies highlight the importance of public clonotypes and their selection in shaping the CD8+ T-cell response against HIV.

**TCR avidity and CD8+ T-cell functional efficacy**

The ability of a T-cell to respond to a defined concentration of cognate antigen, known as its antigen sensitivity (AgS) or functional avidity, has emerged as a major correlate of the functional quality of T-cells [1, 9, 13, 16-19]. Highly antigen-sensitive T-cells are considered to be qualitatively superior, as determined by functional readouts such as cytokine secretion and cytolytic activity. AgS is a multifaceted parameter, influenced by factors relating to both the CD8+ T-cell and its antigen-bearing target (e.g. TCR features, CD8 binding, co-stimulatory and co-inhibitory receptors, epitope quality and expression levels as well as the nature and density of the restricting MHC allele). Since TCR independent factors, such as CD8 co-receptor binding, can contribute significantly to the magnitude and quality of TCR signaling [20], we focus here on the avidity of the TCR, considered independently from its natural microenvironment, and defined as the composite measure of the affinities of individual TCR/pMHC interactions present at the cellular level. Several studies indicate that the avidity of the TCR is a crucial determinant of AgS and therefore of CD8+ T-cell efficacy against HIV. The CD8+ T-cell response against the immunodominant HLA-B*27:05 restricted epitope derived from HIV p24 Gag263-272, KRWIILGLNK (KK10), represents the best-characterized response to HIV-1 [21, 22] and is linked to slower disease progression [9, 23]. In vitro and ex-vivo characterization of KK10-specific CD8+ T-cells isolated from HLA-B*27:05+ HIV-infected individuals, showed that TCR avidity correlated with their ability to respond to antigen with a high degree of AgS and polyfunctionality, and display potent HIV-suppressive activity [9, 13, 18]. Clonotypic analysis revealed that superior TCR avidity was actually a feature of public clonotypes characterized by TRBV4-3/TRBJ1-3 gene rearrangements, highlighting the central role of TCR avidity in determining AgS [13, 18, 24].

The observations made in the KK10/HLA-B*27:05 system were supported by studies of CD8+ T-cell clones specific for the HLA-A*03:01 restricted Nef73-82 QVPLRPMTYK (QK10) and Gag20-29 RLRPGGKKKY (RY10) epitopes [25], as well as for the HLA-A*24:02 restricted RYPLTFGWCF (RF10) and RYPLTFGW (RW8) Nef epitopes [7], which showed a link between TCR avidity and
antiviral efficacy for each targeted epitope. Highly avid oligoclonal CD8+ T-cells specific for the HLA-B*3501-restricted p24 Gag254-262 NPVPVGNIY (NY9) epitope have also been observed in HIV-2 infected individuals characterized by slow disease progression [26]. Furthermore, the importance of TCR avidity for the effective control of SIV infection was highlighted in a recent macaque model study of CD8+ T-cells specific for the immunodominant Mamu-A*01-restricted SIVmac-251 Gag181–189 CTPYDINQM (p11C) epitope [27]. Lastly, the potential therapeutic benefits of engineering high-affinity TCRs directed against HIV-1 antigens have also been demonstrated [28, 29]. For instance, high-affinity variants of a natural TCR specific for the immunodominant HLA-A*02:01-restricted HIV-1 p17 Gag77–85 SLYNTVATL (SL9) peptide, generated by phage display, exhibited higher levels of AgS and polyfunctionality [28].

However, other studies have demonstrated that TCR avidity or even AgS were not necessarily related to CD8+ T-cell efficacy in the setting of HIV-1 infection [27, 30-32]. In line with these reports, two recent investigations into the structure to function relationship of a highly effective public TRAV17/TRBV7-3 TCR specific for the immunodominant HIV-1 Pol283-290 TAFTIPS (TI8) peptide, presented by the protective HLA-B*51:01, showed it possessed low avidity for its cognate antigen [33, 34]. The structural basis for the low affinity was attributed to the notable lack of peptide ‘bulging’ within the MHCI groove, presenting the TCR with a featureless landscape, and the potential for few peptide/TCR contacts [34]. Although rare, low-affinity MHCI-centric TCRs have been previously documented in other systems [35, 36], and display structurally different recognition patterns compared to high-affinity TCRs specific for other immunodominant HIV-1 epitopes [24, 28]. The correlation between TCR avidity, AgS and HIV suppressive capacity may also be blurred by the multiple factors that can affect CD8+ T-cell recognition of cognate pMHCI molecules on the target cell surface, as well as the way AgS is measured. For instance, by measuring AgS in PBMCs or primary cell lines composed of diverse clonotypes, the anti-viral activity of low frequency highly avid clonotypes may be masked by the low to medium avidity response of the bulk T-cell population. Divergent outcomes of different antigen specificities should also be considered. For instance, it may be more advantageous for a T-cell response to target a highly conserved (or abundant) epitope with low avidity than a hypervariable (or rare) epitope with high avidity, due to the low fitness cost incurred by the virus in the latter instance. It is also important to keep in mind that enhancing the TCR/pMHCI affinity above naturally occurring thresholds may not necessarily be useful. Such enhanced TCRs, presenting supraphysiological affinities, may not offer any advantages over their wildtype (WT) counterparts by reaching a plateau of maximal functionality [37], or adversely, resulting in the rapid deletion of the associated
CD8+ T-cells [38]. Lastly, while TCR avidity appears to be advantageous in certain settings, it can also be responsible for driving rapid viral escape [39, 40], T-cell exhaustion [9], loss of polyfunctionality [41, 42] and ultimately disease progression. The existing discrepancies in the data with regards to the importance of TCR avidity for CD8+ T-cell efficacy certainly highlight the fact that other TCR-relevant parameters can also confer protection against HIV.

**TCR crossreactivity and CD8+ T-cell adaptation to HIV evolution**

In order to contain a rapidly evolving retrovirus like HIV-1, an effective CD8+ T-cell response must not only be highly avid, but also have the capacity to recognize escape mutants. Crossreactivity, which gives a measure of the variety of peptide antigens recognized by a single TCR [43, 44], has been reported to delay progression to AIDS, via targeting of escape variants [17, 45]. A comparison of the functional attributes of p24 Gag-specific CD8+ T-cells across an HLA-unbiased cohort of HIV-infected individuals, demonstrated that high levels of AgS and crossreactivity were associated with superior control of viraemia [17, 46]. Furthermore, highly effective clones isolated from elite-controllers were characterized by specific TCR clonotype usage and crossrecognition of viral escape mutants [45, 46]. At the clonal level, the role of crossreactivity in the control of HIV-1 infection is once again best exemplified in the well-characterized KK10/HLA-B*27:05 system. When the immune pressure exerted by high-avidity but monospecific public TRBV4-3/TRBJ1-3 clonotypes drives the emergence of TCR escape mutations, crossreactive TRBV6-5/TRBJ1-1 clonotypes appear in some HIV-1 viraemic individuals to resume viral control [11, 13, 24]. These replacement crossreactive clonotypes retained high TCR avidity, and by having equal preference for the dominant L268M escape mutant and the WT virus, were able to suppress viral replication for a prolonged period of time [11, 13, 24]. Ultimately, the virus may escape the KK10-specific CD8+ T-cell response through a R264K substitution. Although the latter is more difficult to attain due to the requirement of a compensatory mutation to maintain viral fitness, once gained, the R264K mutation drives the escape from even the most highly effective of KK10-specific clonotypes by evading presentation by HLA-B*27:05 (Figure 1A).

Similarly to the KK10 scenario, functionally superior CD8+ T-cell clonotypes responding to the T18 epitope presented on the protective HLA-B*51:01 allele, displayed a high degree of crossreactivity against the common T290V (TV) escape mutant [33]. In this system however, both sets of clonotypes presiding over the control of infection were crossreactive, albeit not to the same extent. While the less crossreactive TRAV8-2/TRBV24-1 clonotypes (with higher affinity for WT than TV
antigen) drove selection of the TV mutant, the highly crossreactive TRAV17/TRBV7-3 TCR clonotypes (with equal preference for the WT and TV antigens), were deployed only on emergence of the TV mutation [33]. Together these partly and fully crossreactive clonotypes were able to maintain efficient control of viral replication, by letting the virus alternate between escape and reversion to WT. The superior crossreactivity exhibited by other public clonotypes has also been described in SIV infection [15]. Moreover, the functional benefits of previously mentioned engineered high-avidity TCRs were attributed precisely to their ability to crossreact and respond to a large panel of escape variants [28, 29]. Ultimately, in order to prove effective against HIV, CD8+ T-cells bearing high avidity TCRs must also possess high levels of crossreactivity, which can either be a feature of the same TCR [28, 29] or be attributed by other complementary clonotypes [11, 13, 24]. Mechanistically, work with overlapping epitopes has shown that TCR crossreactivity is restricted to peptides of a single length [7, 47-49]. One study focusing on the degenerate recognition of the HLA-A*02:01 restricted Gag SL9 epitope showed that amino acid variations at several positions of the peptide resulted in the formation of structurally-similar antigens, which were well tolerated by both the HLA molecule and the SL9-specific TCR [50]. This example illustrates that the specificity of the TCR can be determined by the conformation of the MHC-bound peptide backbone rather than the amino acid side chains. However, structural insights into the basis of crossreactivity have not revealed a common rule; moreover both low [7, 33, 34] and high [13, 24, 28, 29] avidity TCRs can be crossreactive. Since crossreactivity is determined by the TCR, peptide antigen and the restricting MHCI allele, further evidence is required to build up a better picture of this complex functional parameter.

Although TCR crossreactivity represents a valuable qualitative attribute to the control of HIV-1 replication via recognition of escape mutants, reshuffling of the entire CD8+ T-cell repertoire may be required in order to keep pace with the frightful speed of viral evolution in vivo. These so-called “clonotypic shifts”, allow the HIV-specific CD8+ T-cell repertoire to adapt to changes in the spectrum of viral antigens being presented at any given time. A recent study monitoring the relationship between viral evolution and TCR repertoire diversity in a cohort of untreated HIV-infected individuals, demonstrated the importance of continuous bidirectional adaptation between virus-targeting CD8+ T-cells and HIV, in delaying disease progression [51]. The dynamic interplay between viral evolution and clonotypic turnover has also been documented at the level of individual clonotypes, targeting specific viral escape mutants. In addition to the above mentioned work on KK10/HLA-B*27:05 clonotypes [13], the molecular mechanism behind the clonotypic adaptation to the mutational escape of two superimposed HIV-1 Nef-derived immunodominant epitopes RW8
(RYPLTFGW) and RF10 (RYPLTFGWCF), both presented by the HLA-A2*24:02 allele has recently been investigated [7]. Following the emergence of the Y_{139}F mutation within these epitopes upon selection pressure from both RW8 and RF10-specific CD8\(^+\) T-cells, the recruitment of a new clonotypic repertoire is only observed in response to the YF-RF10 variant (Takiguchi and colleagues, unpublished). Importantly, the inability of the YF-RW8 mutant to evoke similar changes in the RW8-specific CD8\(^+\) T-cell repertoire was attributed to the featureless structural conformations of WT- and YF-RW8 epitopes, when bound to HLA-A\(^*\)24:02. Since recognition of featureless pMHC landscapes may facilitate TCR crossreactivity [33-36], the highly crossreactive RW8-specific clonotypes were able to preempt the emergence of the YF-RW8 mutant, requiring no further adaptation to achieve control of HIV-1 replication (Takiguchi and colleagues, unpublished). However, in addition to affecting TCR binding, the YF mutant, also lowers the stability of the pMHC complex, and therefore TCR avidity, independently of any clonotypic adaptation (Figure 1B). This represents a definitive advantage for the virus, which likely explains the accumulation of this variant at a population level.

**TCR repertoire analysis of CD4\(^+\) T-cells in HIV infection**

Early studies of the total CD4\(^+\) T-cell compartment revealed that a loss of TCR repertoire diversity correlated with disease progression and viral load, and that repertoire diversity was only partially restored upon anti-retroviral treatment [52-54]. However, these repertoire perturbations appeared less prevalent in CD4\(^+\) than in CD8\(^+\) T-cell subsets during primary infection, presumably, due to CD4\(^+\) T-cells being less prone to undergoing massive clonal expansions. A more recent study carried out at the CD4\(^+\) T-cell subset level reported only minimal changes in TCR diversity. This commonly observed loss of diversity was attributed to changes in subset distribution and absolute CD4\(^+\) T-cell number [55]. While the diversity of the CD4\(^+\) T-cell repertoire may be maintained in most cases at level deemed sufficient for immune reconstitution upon anti-retroviral treatment, the quality of the reconstituted repertoire may nevertheless remain suboptimal. This is reflected by the low AgS of Gag-specific CD4\(^+\) T-cells in successfully treated patients [56]. However, the study of the HIV-specific CD4\(^+\) T-cell TCR repertoire has been both lacking and lagging behind that of their CD8\(^+\) counterpart, so that data on the clonotypic composition and TCR function of the HIV-specific CD4\(^+\) T-cell population remain scarce. This is to a large extent due to a prior unavailability of reliable tools, such as MHC class II tetramers (employed for the \textit{ex-vivo} detection of HIV-specific CD4\(^+\) T-cells) as well as the relative scarcity of these cells in HIV-infected individuals. A number
of studies have indeed documented the early functional impairment and/or loss of HIV-specific CD4+ T-cell responses in progressive infection [57-59].

In contrast, the HIV-specific CD4+ T-cell response appears to be quantitatively and qualitatively different in the setting of controlled HIV infection. Proliferation [60], low expression of co-inhibitory receptors [61], polyfunctionality [62], and persistence of the central memory and terminally differentiated effector memory CD4+ T-cell phenotypes [63] have indeed been reported in HIV controllers. There is also evidence for the cytotoxic function of CD4+ T-cells, via direct killing of HIV-infected cells [64-66], which has been associated with slower disease progression [67]. The preserved HIV-specific CD4+ T-cell responses in controllers have therefore enabled a more precise characterization of these cells. In this unique group of patients, CD4+ T-cells preferentially target Gag rather than Env epitopes, indicative of intrinsic differences in their HIV-specific TCR repertoire compared to progressor patients [68, 69]. In addition, their Gag-specific CD4+ T-cells were shown to maintain high AgS and TCR avidity [56], qualitative features that may account for the superior functional efficacy of these cells. Accordingly, higher AgS of HIV-specific CD4+ T-cells has been associated with increased polyfunctionality [18]. Emerging evidence suggests that key features distinguish the clonotypic repertoires of CD4+ T-cells found in controllers from that of patients requiring anti-retroviral treatment. Indeed, controller CD4+ T-cells specific for the most immunodominant epitope in Gag (a.a. 293-312) are characterized by a strongly biased TCR repertoire, enriched for public clonotypes (Chakrabarti and colleagues, unpublished). The most prevalent of these public clonotypes, when tested functionally, recapitulate the properties characteristic of the controller CD4+ T-cell response (i.e. high TCR avidity, high AgS, and polyfunctionality). Overall, this suggests that highly avid, Gag-specific public clonotypes may shape the properties of the CD4+ T-cell response in controlled HIV infection. Whether such clonotypes are selected exclusively in controllers, or whether they are also selected but then rapidly lost in progressor patients remains an open question.
Conclusion

The nature of the TCR emerges as a main determinant of CD8+ T-cell function and efficacy against HIV. It endows CD8+ T-cells with the capacity to recognize WT and mutant HIV epitopes alike, with high affinity, whilst conferring potent effector functions to eliminate virally-infected cells. Emerging evidence also imparts a similar importance of the TCR to the HIV-specific CD4+ T-cell response. Moreover, in addition to the study of individual TCR-antigen interactions, we are beginning to appreciate the importance of the TCR repertoire in the long-term maintenance of cellular immune efficacy against HIV. Adaptation to a rapidly evolving virus through the recruitment of new clonotypes is indeed vital for a potent cellular immune response, capable of countering the emergence of TCR escape mutants. Nevertheless, we are still some way off from understanding the complexity behind the forces that sequentially drive viral evolution and host immune adaptation during the course of HIV infection, the so called “molecular arms race” between the immune system and viruses like HIV. Furthermore, the impact of clonal exhaustion, an irreversible loss of effective T-cell clonotypes, on the long-term maintenance of effective immunity, needs to be considered. This is of particular importance in the context of increased cell turnover, associated with high TCR avidity and persistent antigenic stimulation. The study of T-cell priming capacity (i.e. the induction of de novo T-cell responses) and the factors that determine the selection of specific clonotypes (e.g. TCR activation threshold and precursor frequency) is therefore essential. The implementation of cutting-edge technological advances to perform single cell level studies, implicating multi-parametric flow cytometry, molecular profiling and TCR repertoire analyses, alongside deep sequencing of the viral genome, is needed to address these questions. Moreover, although T-cell quality and anti-viral efficacy appear to relate primarily to the nature of their TCR, it is important to assess the contribution of co-stimulatory and co-inhibitory receptors. Alternatively known as immune checkpoints, these regulatory molecules assist in the fine-tuning of T-cell effector functions, as well as influencing cell metabolic state. Assimilating these new data will be key to the development of effective immunotherapeutic strategies, such as the induction of high avidity T-cells through vaccination or their maintenance via immune checkpoint manipulation. Only then will we be capable of fully suppressing HIV replication and, better still, eradicating viral reservoirs altogether.
Highlights

- TCR repertoire studies reveal specific immunodominance patterns and public clonotypes within HIV-specific CD8⁺ T-cell populations
- TCR avidity is a major determinant of the sensitivity of CD8⁺ T-cells to HIV antigens, and therefore their functional efficacy against the virus
- Recruitment of clonotypes crossreactive for wildtype and mutant viral epitopes is a key requirement for adaptation to HIV evolution and long-term control of viral infection
- High affinity public clonotypes may shape the properties of the anti-viral CD4⁺ T-cell response in HIV controllers

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References


Figure legend

**Figure 1. HIV evolution and CD8+ T-cell adaptation at the clonotypic level**

The figure illustrates the changes experienced by the virus and the CD8+ T-cell response specific for (A) the HLA-B*27:05 restricted KRWIILGLNK (KK10) Gag epitope, and (B) the HLA-A*24:02 restricted RYPLTFGWCF (RF10) and RYPLTFGW (RW8) Nef superimposed epitopes.