Title

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Journal

Current Opinion in HIV and AIDS, 17(6)

ISSN

1746-630X

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Publication Date

2022-11-01

DOI

10.1097/coh.0000000000000765

Peer reviewed

HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2022 November 01; 17(6): 333–337. doi:10.1097/COH.0000000000000765.

HIV T-cell immunogen design and delivery

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Abstract

Purpose of the review: Not all T cell responses against HIV are created equally and responses of certain epitope specificities have been associated with superior control of infection. These insights have spurred the development of a wide range of immunogen sequences, each with particular advantages and limitations.

Recent findings: We review some of the most advanced designs that have reached or are close to reaching human clinical trials, with a special focus on T-cell immunogen developed for therapeutic use. We also touch upon the importance of how immunogens are delivered and point out the lamentable fact that there is essentially no alignment between different designs and vaccine regimens, which is a major hindrance to accelerated advances in the field.

Summary: The design of an immunogen able to induce T cell responses of adequate specificity and functionality is subjects to a wide range of pre-clinical and clinical studies. Few designs have shown promise to date, but emerging data highlight the critical contribution of specificity to effective antiviral activity in vivo.

Keywords

T cell immunogen; Epitope specificity; Clinical trial; Vaccine delivery

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Conflict of Interest: C. Brander is coinventor of the HTI immunogen and cofounder, shareholder and CSO of Aelix Therapeutics. D. Hartigan-O'Connor is cofounder and shareholder of Tendel Therapies Inc.

Introduction:

Robust, broad and functionally competent T cell responses against HIV have been suggested to contribute to in vivo control of viral replication. Although specific, functional T cell immune correlates of controlled HIV infection remain elusive, a large number of studies have linked T cell poly-functionality, functional polarization, HLA restriction and epitope specificity with controlled HIV infection[1,2]. These observations have given rise to a multitude of approaches for HIV vaccine immunogens, designed to elicit more effective T cell responses to the virus. In addition, several strategies that are informed on viral sequence characteristics have been developed and in some cases have reached clinical testing, particularly in the therapeutic vaccine area (https://www.avac.org). It is also likely that aside from the vaccine immunogen design, its mode of delivery, vector choice, vaccination regimen and intervals may also prove decisive for the induction of an effective and lasting T cell immunity. Unfortunately, pre-clinical and clinical studies generally don't share the same vectors, vaccination regimens or study populations, so that comparing the efficacy of different immunogens is difficult, to say the least. Furthermore, despite some international efforts, the end point of clinical studies, especially in the therapeutic use of T cell vaccines vary widely, further complicating direct comparisons between different immunogen designs[3]. As a consequence, rare encouraging data are not integrated in subsequent studies of other strategies, causing an extraordinary amount of resources being directed towards many different, parallel developments without fertilizing cross-talk.

The importance of T cell specificity for effective antiviral T-cell responses:

Since the identification of T cell responses to HIV by Walker and Plata more than 35 years ago, there has been an ongoing debate on the relative contribution of these responses to virus control in vivo[4,5]. Given the high and rapid rate of viral adaptation to T cell immunity, the in-vivo effectiveness of virus-specific T cells has been questioned. In addition, already early studies of in vitro inhibition of viral replication by in-vitro expanded, epitope-specific T cell clones showed clear variable ability of these cells to suppress viral growth, suggesting that epitope-specificity could play a role in antiviral immunity[6,7]. These observations have been validated many times since by studies determining the fine specificity of virus-specific T cell responses in HIV infected individuals. These results have shown the beneficial effect of mounting T cell responses to Gag and Pol proteins in HIV controllers, compared to responses in HIV-noncontrollers that are predominantly targeting epitopes in more variable proteins such as HIV Envelope and Nef[1,8,9].

Immunogen design informed by functional T cell response data:

One of the above studies have given raise to the HTI immunogen, which has recently shown a clinical efficacy signal in the therapeutic vaccine setting in early treated HIV infected individuals[10]. The HTI design is based on the identification of T cell responses and specificities predominantly detected in individuals with low HIV viral load and differentiating those from responses that dominate the T cell immunity to the virus in individuals with high viraemia[11]. These studies were conducted in more than 1000 individuals of different ethnicities and viral clades, identified beneficial regions in Gag, Pol and interestingly, in Vif, a protein that has rarely being considered for immunogen

design[11, 12]. Of note, the beneficial regions targeted by HIV controllers were more conserved even when comparing beneficial to non-beneficial regions within HIV Gag p24, which overall is already quite conserved[11]. In its final design, the HTI immunogen consists of roughly 500 amino acids and contains more than 100 well-defined, optimal T cell epitopes, restricted by at least as many different HLA class I alleles[13]. In clinical testing, it induced very broad T cell responses to the immunogen, possibly due to the inclusion of preferred antigen processing sites between the individual 16 segments. The recently reported results from the clinical trial AELIX-002 also showed prolonged viral control in vaccinated individuals compared to placebo recipients, providing the strongest clinical efficacy signal reported to date[10]. Importantly, as the design of the HTI immunogen was based on the testing of hundreds of HIV infected individuals, HLA bias towards beneficial HLA alleles was not observed in its design nor in the clinical efficacy signal. In fact, the clinical signal was enhanced when the analyses were excluding individuals with HLA class I alleles that have been associated with spontaneous control of the infection (e.g. HLA-B27, -B57 and others)[10]. This also suggest that basing the initial immunogen design on sufficiently large human cohorts may be critical to avoid such HLA bias and controlling for its effect in early clinical phases of testing also may be warranted.

Immunogen designs informed by sequence conservation:

Other immunogen designs have been informed by a mixture of viral sequence data and T cell immune reactivity profiles. One prominent example, which also has entered clinical testing is the Conserved region approach pioneered by Hanke and colleagues in Oxford. The design originated from early strategies referred to as HIV-Cons, which consisted of a compilation of long, conserved regions across the viral proteome of different clades, including segments in Gag, Pol and Envelope[14]. The HIV-Cons immunogen was employed in a series of clinical trials, including the BCN02 trial of therapeutic vaccination, where 32% of participants showed relative virus control for up to 32 weeks after antiretroviral treatment was stopped[15]. The newer version of the immunogen (HIVConsVx) includes the conserved segments in Gag and Pol as well as the beneficial regions identify by Mothe et al[11] and provides sequence coverage by using different HIV clade-specific regions[16]. Interestingly, the design uses different immunogen constructs where the individual segments were scrambled in different order, so that potential responses to junctional sites between the segments are not being boosted by repeat vaccination. Pre-clinical analyses demonstrate strong and broad immunogenicity and the immunogen has entered clinical testing in early infection cohorts[16] and NCT04553016. As is true of HTI, the HIVConsVx immunogen does not include Envelope sequences, which have been considered as potentially problematic due to their ability to shift vaccine-induced responses towards (immunodominant) decoy targets[17, 18]. At least one ongoing clinical trial is testing this important concept to assess whether the presence of Envelope sequences in a therapeutic DNA-based vaccine blunts the responses to Gag- and Pol-derived epitopes[NCT03606213]

In addition to strategies that incorporate T cell reactivity data into their designs, several groups have worked on approaches that rely exclusively on viral sequence data. This includes the conserved element (CE) design by Mullins and colleagues, which is based on the identification of the most conserved segments in HIV Gag[19,20]. The design includes

seven Gag segments that are highly conserved across group M virus sequences, all containing defined T cell epitopes restricted by a wide range of HLA class I molecules. Further analysis in groups of HIV controllers and non-controllers showed that several of these elements were indeed frequently targeted by HIV controllers, raising the possibility that CE vaccines could elicit similar responses across a wide range of HLA class I diversity[21]. Indeed, very recent data show the induction of strong responses in NHP upon a DNA/RNA prime regimen, with the induction of both, CD4 and cytotoxic memory CD8 T cells[22,23]. A clinical trial testing this immunogen design in combination with a TLR9 agonist and bnAb treatments is ongoing. NCT04357821

Networked residues approaches:

Another currently explored immunogen design based on sequence analysis is the one by Gaiha et al, who have identified "networked" residues across the viral proteome for their inclusion in an immunogen sequence[24]. The most highly networked residues sit atop a hierarchy that is defined by the web of structural interactions between residues. Such networked residues show co-evolution with many other residues in the viral proteome and may play important roles in viral replicative fitness. It is thus thought that the potential benefit of targeting such residues and epitopes spanning such regions lies in its effect of limiting viral evolution and viral escape from vaccine induced responses. As viral escape from T cell responses is widespread, if not essentially universal, such a strategy may have indeed merit as this may cause significant reduction in viral replicative fitness if the virus has to adapt to the vaccine-induced immune pressure[25,26]. However, the level of conservation and inter-residue "networking" does not necessarily imply immunogenicity and it will be important to test the recognition of regions with highly networked residues in natural infection or to at least demonstrate the presentation of highly networked epitopes by HLA class I molecules on the surface of infected cells[27]. If not, strategies that don't incorporate some T-cell reactivity criteria run the risk of inducing responses to targets that are not effectively processed or sub-optimally presented in naturally infected cells.

Immunogen designs to cover sequence diversity and autologous and rare variants:

Finally, additional approaches to cope with and possibly limit T cell escape include strategies that incorporate multiple sequence variants of the targeted regions. The HIVConsVx approached by Hanke does achieve this to some degree but it's not designed to cover subdominant and very rare variants[16]. From a global-sequence-coverage point of view, this may not be a major limitation but it could well be that rarer variants could elicit stronger and more broadly cross reactive T cell specificities than the most common viral sequences that have become most common precisely because they don't induce effective immunity against the virus. These kind of designs are covered by different strategies, such as the PTE approaches and Mosaic designs and specific web-based tools have been developed that facilitate immunogen design[28,29]. For instance, the Epigraph algorithm by Korber and colleagues can be used across diverse input viral sequences and, by choice, can be made to ignore very rare sequences, which does not significantly reduce population coverage. Other approaches that include subdominant sequence variants include personalized vaccine approaches, similar to the ones that are being developed for instance by the HIVACAR consortium (https://cordis.europa.eu/project/id/731626/reporting). Their design combines

autologous Rev and Tat sequences with unescaped HLA-matched optimal CTL epitopes in Gag and Pol in their autologous immunogen sequence. Since in HIVACAR the coverage of autologous epitope variants is limited to at least 20% representation in autologous viral sequences, it will not include rare autologous sequence variants either, which could in theory range from highly immunogenic to antagonistic variants[30, 31, 32]. As no currently developed design test this in clinical studies, it remains to be seen how responses specifically elicited by rare(st) variants will perform in the clinical setting and what cross-reactivity potential such responses could have. Similarly, the clinical benefit of delivering multiple sequence variants of the same immunogen remains to be shown. In any case, inducing responses with more than one sequence has shown in pre-clinical models the ability to induce responses with superior depth of epitope recognition[33]; a feature that could critically contribute to vaccine efficacy, especially when targeting more variable segments of the virus.

Immunogens targeting alternative viral T cell antigens:

While glycosylation sites and glycosylation immunology are commonly considered for B-cell immunity and may be important for the effectiveness of the humoral immunity upon HIV vaccination, it has largely been neglected in regards to T cell responses. Past studies have however shown that glycosylation marks on T cell epitopes can not only survive the antigen processing machinery but can also be maintained on presented epitopes and recognized by epitope-specific T cells[34, 35]. Recently, Olvera et al analyzed such occurrences in HIV infection and found evidence that glycosylation and mutated glycosylation sites could indeed impact T cell reactivity to the virus[36]. Important in this regard is that recombinant proteins, depending on their production cell line, may not carry such glycosylation modifications and thus fail to induce these responses. Equally, subunit immunogens expressed off a vaccine vector may not follow the same intracellular protein transport pathways and may thus not undergo the same post translational modifications as do the natural viral proteins, again failing to induce responses that are induced by naturally produced and post translationally modified viral proteins in an infected cell. Despite the indirect evidence provided by Olvera and colleagues, the potential importance of such T cell responses to glycosylated epitopes clearly merits further investigation. Equally missing from current immunogen designs are responses to potential cryptic T cell epitopes, such as epitopes in frame-shifted sequences and in protein sequences encoded by alternative reading frames. Such protein sequences have been identified and shown to harbor CTL epitopes[37, 38]. Indeed, T cell responses against these epitopes are able to inhibit viral replication in vivo and leave a specific HLA footprint on the viral sequence[37]. However, they don't seem to contribute in a major manner to viral evolution in the early stages of acute infection[39]. Clearly, similarly to the glycosylated epitopes, the potential of such responses in vaccine design has not been established.

As eluded to above, vaccine immunogen delivery /vector choice will have an important impact on vaccination outcome and effectiveness of antiviral immunity. The surprising results of investigations into RNA immunogenicity for T cells speaks to the great importance of such vector choice for modulating both, the intensity and character of the response. Despite the power of RNA vaccines for inducing antibody responses, both a recent publication[22] and our unpublished work in non-human primates show that RNA priming can

in many circumstances elicit comparatively poor T-cell responses. It is commonly observed that among groups of animals receiving serial mRNA vaccination, whether expressing intracellular or secreted antigens, impressive antibody responses testify to robust gene expression from the vaccine—while T-cell responses among PBMC remain anemic (<0.1%) or, in some animals, absent. Animals receiving DNA[22] or adenovector priming followed by mRNA boosting, however, manifest very satisfactory T-cell responses, which can exceed those that achievable with DNA and adenovectors. The role of the vector in a vaccine regimen therefore goes far beyond gene expression to encompass profound influence on the character of the response. Within the confines of the T-cell compartment, as well, there is significant variation. RhCMV/SIV and other herpesvirus vectors elicit an impressive response in both the CD4 and CD8 compartments, while adenovectors are heavily CD8 biased[40,41,42]. Within the CD8 compartment, only RhCMV/SIV vectors are capable of eliciting cells restricted by Mamu-E or class-II MHC [43]. However, there is a wide range of vector-influenced, subtler variation in polyfunctionality[44], cytotoxicity[45,46], durability, and stem-like expansion potential[47].

Conclusions:

While incremental advances have been made in the understanding of functional correlates of immune control of HIV, translating this understanding into the design of effective T cell immunogens has been slow. Through large cohort studies, we and others have shown the fine specificity of virus-specific T cells to be a major component of effective antiviral cellular immunity. Several immunogen designs aim to capitalize in on this observation, but their relative value remains to be determined through human clinical testing.

Financial support:

This work was supported by USA National Institutes of Health (NIH) - National Institute of Allergy and Infectious Diseases - P01 Research Program Project Grant 1P01AI131568-01 to CB and DJHOC and funding from the European Union's Horizon 2020 research and innovation program under grant European AIDS Vaccine Initiative 2020 (EAVI2020) #GA681137 to CB.

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Key points:

- HIV infection induces broad and strong T cell responses, which are unable to control the virus in natural, progressive infection.
- Immunogen design thus needs to be restrictive, i.e to focus on responses that support control over viremia, rather than all-inclusive.
- Several immunogens attempt to test this concept, with some promising data emerging from phase II therapeutic vaccine trials.