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Vaccine-induced V1V2-specific Antibodies Control and or Protect against Infection with HIV, SIV and SHIV

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Abstract

Purpose of review: In humans, only one independent immunologic correlate of reduced risk of HIV infection has been identified: a robust antibody (Ab) response to the V1V2 domain of the gp120 Envelope (Env) protein. In recent years, the presence and level of V1V2-specific Abs has also been correlated with protection from SIV and SHIV infections. Here we review the multitude of studies showing the *in vivo* protective effects of V1V2 Abs and review their immunologic characteristics and anti-viral functions.

Recent findings: Structural and immunologic studies have defined four epitope families in the V1V2 domain: one epitope family, V2q, which preferentially present as a quaternary structure of the Env trimer, and another epitope family (V2qt) which requires the quaternary trimeric Env structure; these two epitope types are recognized by two families of monoclonal Abs (mAbs) —V2q- and V2qt-specific mAbs—which display broad and potent neutralizing activity. A third epitope family, V2i, is present as a discontinuous conformational structure that overlays the α4β7 integrin binding motif, and a fourth epitope family (V2p) exists on V2 peptides. Antibodies specific for V2i and V2p epitopes display only poor neutralizing activity but effectively mediate other anti-viral activities and have been correlated with control of and/or protection from HIV, SIV and SHIV. Notably, V2q and V2qt Abs have not been induced by any vaccines, but V2p and V2i Abs have been readily induced with various vaccines in non-human primates and humans.

Summary: The correlation of vaccine-induced V2p and V2i Abs with protection from HIV, SIV and SHIV suggests that these Ab types are extremely important to induce with prophylactic vaccines.

Keywords

vaccines; V2; antibodies; non-human primates; epitope; anti-viral functions

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INTRODUCTION

The key to the rational design of an effective HIV vaccine depends on the identification of immune correlates of protection and immunologic mechanisms that prevent HIV acquisition. The first independent correlate of reduced risk of HIV infection in humans was identified by studies of participants in the RV144 clinical vaccine trial: a robust antibody (Ab) response to the V1V2 region of the virus gp120 envelope (Env) glycoprotein. Similar correlations were subsequently identified in studies of non-human primates (NHPs) between protection from SIV and SHIV and V2 Ab levels. Here, we summarize these human and NHP findings and the V2 Abs that are involved in the control of and/or protection from HIV, SIV and SHIV.

Structural and immunologic characterization of the V1V2 domain.

Studies of polyclonal sera from HIV-infected individuals have established that, over time, infection generates different “humoral fingerprints” (1). This is true for patterns of Ab specificities, subclasses, and anti-viral activities (2–6). Similar findings pertain to Abs induced by vaccines targeting SIV (7, 8) and SHIV (9–12). Given the association between V2 Abs and protection in human and animal models, it is critical to understand the complexity of the V1V2 domain of the virus Env and the Ab response to it.

Conformational complexity of V1V2.—In HIV, the V1V2 domain, like the rest of gp120, exhibits marked conformational flexibility. The V1V2 domain serves as the “trimer association domain” at the apex of the closed trimeric Env, but the V1V2 domain of each of the three gp120 protomers opens out when gp120 interacts with CD4 (13–16). The C-strand of V2, composed of amino acids (AAs) 170–176, one of the five strands composing the V1V2 beta-barrel, exists in different conformations, varying between a beta-strand and an alpha-helix (17–19), where the beta-strand configuration is preferentially present in the closed, structurally constrained trimeric Env while the alpha-helical conformation is preferred where there is less structural constraint when the Env is fully open. The preferred configuration is undoubtedly affected by (a) the sequence of V1 and V2, (b) substitutions at key residues, (c) the molecular context in which the V1V2 domain is placed, and (d) the intra- and inter-protomer interactions of V1V2 within the Env trimer (20).

Alternative V2 conformational epitopes.—As a result of this configurational complexity, there are at least four types of epitopes in the V1V2 region as shown in Figure 1: (a) **V2q** epitopes which preferentially recognize structures formed by the **q**uaternary interaction of the three gp120 protomers and are glycan-dependent; V2q is recognized by V2q mAbs such as PG9 and PG16 (17, 21–24), (b) **V2qt** epitopes which recognize **q**uaternary, **t**rimer-dependent V2 epitopes at the apical center of Env are recognized by several V2qt mAbs exemplified by PGT145 (25), (c) **V2i** epitopes which overlay the α4β7 **i**ntegrin binding site in V2 and are recognized by V2i mAbs such as 830A and 2158 (26–28), and (d) **V2p** epitopes which are presented by V2 linear and cyclic **p**eptides, and recognized by V2p mAbs such as CH58 and CAP228–16H (19, 29, 30). The V2q, V2qt and V2i mAbs preferentially recognize their various epitopes when the C-strand of V2 is in the beta-strand conformation. In contrast, V2p mAbs recognize the C-strand in its alpha-helical configuration (19). These four families of mAbs that recognize the various V1V2 epitopes

display distinct patterns of reactivity; an example is shown in Figure 2 in which the patterns of reactivity of V2p and V2i mAbs are shown vs. a panel of eight V2 bearing antigens.

The correlates of reduced risk in RV144.

RV144 is the only clinical vaccine trial to date which provided a marginal but statistically significant reduced rate of infection (31) as well as an independent correlate of risk (COR) of HIV infection: an inverse relationship between the incidence of infection and the level of Abs binding to a $V1V2_{CaseA2}$-gp70 fusion protein (32–34). The $V1V2_{CaseA2}$-gp70 fusion protein preferentially reacts with V2i mAbs, and indeed, several V2i mAbs have been selected from the cells of HIV-infected individuals using this reagent, and these V2i mAbs are highly cross-clade reactive (35, 36). In this context, it is noteworthy that while $V1V2_{CaseA2}$-gp70 carries the V1V2 sequence from a clade B strain (44), infections occurring in the RV144 participants were primarily due to clade AE (CRF01_AE), the predominant circulating strain in Thailand, and this supports the hypothesis that the V2 Abs implicated in the inverse COR were cross-clade reactive.

Notably, in human vaccine studies other than RV144, the induction of highly reactive and functional V2-specific Abs has not been strong, e.g., in studies such as VAX003, VAX004 and HVTN100 (5, 37, 38). It is hypothesized that the gp120 of the clade AE A244 strain used in RV144 is unusual in its ability to efficiently induce V2 Abs. Thus, for example, the immunogens used in HVTN100 (ALVAC-HIV [vCP2438] and bivalent Subtype C gp120s [1086 and TV1]), which was the precursor of the on-going Phase III HVTN702 study in South Africa, induced a markedly poorer V2 response than that attained in RV144 (39). These findings are of particular interest in the context of recent studies in which robust V2i and V2p Ab responses have been elicited using V2-targeting vaccine constructs in rabbits (40, 41) and NHPs (42). Notably, in the latter study, the use of a trimeric $V1V2_{A244}$-scaffold fusion protein as part of an immunogen cocktail appeared to be particularly effective in inducing broadly reactive and functional V2 Abs.

In addition to the inverse COR with V2i Abs, a similar role for V2p Abs has been documented. Thus, studies with plasma from RV144 vaccinees demonstrated an inverse COR in terms of the Ab response to linear V2 peptides tested by microarray (43), and the correlations of Abs cross-reactive with V2 peptides representing different HIV clades were at least as significant as the correlation seen with the primary variable generated using the $V1V2_{CaseA2}$-gp70 fusion protein. As noted, linear and cyclic V2 (cV2) peptides preferentially assume a structure when complexed with specific V2p mAbs in which the C-strand is in an alpha-helical configuration (19, 29, 30), and two such V2p mAbs were isolated from circulating cells of an individual receiving the RV144 vaccine regimen (19). Thus, we know from polyclonal and mAb studies emanating from RV144 that V2p Abs recognizing the alpha-helix in the C-strand of V2 were induced by the RV144 vaccine and that they constitute an inverse COR ((43) and Table 1). Additional V2p mAbs have recently been isolated from individuals infected with clade C (29, 30). All of these V2p mAbs have been crystallized and reveal the targeted epitope in the V2 C-strand as an alpha-helix or helix-loop, and, like the plasma V2p polyclonal Abs in RV144 vaccinees (33), these mAbs are cross-clade reactive (Figure 2A). (44)

The role of V2 Abs in the control of and protection from SIV and SHIV infections in non-human primates.

The original observation of an inverse COR in RV144 has been supported by many subsidiary studies of the RV144 data (3, 4, 43, 45, 46). Nonetheless, there are critics who remain skeptical of the RV144 correlates analyses (47). This skepticism is now tempered by both active and passive immunization studies from many labs showing correlates of protection from SIV and SHIV infection with the presence of V2 Abs (Table 1).

V2p-specific Abs protect against SIV infection.—In an NHP vaccine study using vaccine regimens consisting of Ad26 and/or modified vaccinia Ankara (MVA) vector-based vaccines expressing SIV_{SME543} gag, pol and Env antigens with subsequent intra-rectal (i.r.) challenges with SIV_{mac251}, there was a ≥80% reduction in per-exposure probability of infection (48). The strength of Ab binding to a biotinylated cyclic V2 peptide from SIV_{SME543} correlated positively with the number of challenges required to establish infection ($p< 0.0001$).

Another NHP study utilized priming with gp160 DNA from SIV_{mac239} and boosting with recombinant $Ad5_{SIVmac239}$ with subsequent multiple mucosal challenges with SIV_{E660} (49). Among the significant humoral response correlates identified was the strength of binding of plasma IgG Abs to a $V1V2_{SIVmac239}$ linear peptide with time to infection ($p=0.009$). In this study, a sieving effect was also noted at a glycosylation site in V1V2 that conferred neutralization resistance. This is similar to the sieving signature identified in the RV144 human trial (45).

Additional studies in NHPs also support the role of V2-specific Abs in protection from or control of SIV. With sera from animals immunized with a regimen similar to that used in RV144, Ab assays revealed that the reduced risk of SIV_{mac251} acquisition correlated with the presence of mucosal IgG to cyclic V2 ($p=0.0018$) (50, 51). In yet another study, where animals were immunized with gp120 protein and human papilloma pseudoviruses expressing SIV_{mac251} genes +/− ALVAC-SIV_{mac251}, a significant correlation was found between the number of challenges to achieve persistent infection with SIV_{mac251} and the avidity index for V1V2 Abs in blood ($p=0.014$) (52). And most recently, in NHPs immunized with SIV_{mac251}-derived *env* plasmids and monomeric M766 gp120 protein followed by challenge with SIV_{E660}, inverse correlations were identified for (a) plasma and mucosal V1V2 responses with peak viral load ($p=0.05$ and $p=0.01$, respectively), (b) responses to cyclic V2 peptides with post-peak and chronic viremia ($p=0.01$ for each), and (c) V2-specific responses with delayed virus acquisition and post-infection control (53). Each of these experiments suggests that Abs that hampered SIV infection were of the V2p type which recognize the alpha-helical V2 C-strand configuration

V2p Abs protect against SHIV infection.—Most recently, an RV144-like vaccine regimen was tested in NHPs that were challenged with $SHIV_{BaL}$ (54). All three unimmunized animals were infected after two i.r. challenges, but in five of the nine immunized macaques, tight control of viremia was noted as reflected by only transient and low plasma viral load measurements, with no measurable virus in tissues at necropsy 13

weeks after challenge. Luminex studies of the plasma from these animals showed a correlate of protection from $SHIV_{BaL}$ with Abs of the V2p type that were reactive with $V1V2_{1086}$-tags (19), a reagent in which the V2 C-strand preferentially adopts an alpha-helical conformation as shown by circular dichroism (55).

The role of V2i Abs in SHIV viral control.—To date, only indirect, correlative data have linked V2 Abs with protection in human and NHP experiments. The first direct *in vivo* test of the hypothesis emanating from RV144—that V2 Abs could reduce the risk of infection—was reported recently in experiments investigating the role of a passively administered V2i mAb in protection from, and/or control of infection in NHPs challenged i.r. with $SHIV_{BaL}$ (56). NHPs received three weekly doses at 10 mg/kg of the IgG1) isoform of the V2i mAb 830A (n= 12, while control animals (n=12) received a dengue-specific mAb (DEN3) at the same times and doses. Animals were challenged with $SHIV_{BaL}$ twice during each week that they received the passively transferred mAb. Blood specimens were drawn at regular intervals at the time of and after challenge, and animals were sacrificed and necropsied six weeks after infection. On the basis of SIV_{gag} RNA copies/ml in plasma, 11/12 control animals were infected by the sixth and final $SHIV_{BaL}$ challenge dose, and while the twelfth animal had no detectable plasma viral load (PVL), SHIV was detected in its liver at necropsy. Of the 12 animals receiving V2i mAb 830A, three had no detectable PVL at necropsy and no SIV_{gag} DNA was detected in their tissues. Of these latter three macaques, one was plasma aviremic after all challenge doses and two had only low and transient positive PVLs at a single time point. Compared in a grouped analysis, the PVL in the 830A recipients was significantly lower than that in the DEN3 controls ($p = 0.031$). The cell-associated viral load (CAVL) DNA in peripheral blood mononuclear cells was assessed as virus copies collected during the course of the experiment, and a statistical analysis revealed a significant difference in CAVLs between controls and the 830A group ($p = 0.038$). In addition, copy numbers of viral DNA in 13 different tissues were measured at the time of necropsy and revealed significant differences in the viral DNA loads between viremic 830A-treated and control macaques ($p = 0.017$). Copy numbers of SIV_{gag} DNA associated with each tissue sampled from the 830A-treated macaques were compared individually to the corresponding tissue from animals in the control group and again significant differences in copy numbers were found in iliosacral, axillary and inguinal lymph nodes and from mixed tissues from the reproductive tract. Thus, while too few animals remained uninfected in the treated group to achieve statistical significance in terms of the risk of infection, the data demonstrate that the presence of the passively administered V2i 830A mAb had significant effects against SHIV challenge in macaques by reducing the viral infectious titer so that animals were either not infected or experienced lower level virus production in blood and tissues resulting in significantly delayed infection, reduced plasma virus load, and decreased viral DNA in lymphoid tissues. This is the first direct demonstration showing the ability of V2i Abs to impede SHIV infection (56).

The biologic functions of V2 antibodies.

Neutralizing Abs were not an inverse COR in the RV144 vaccine trial, suggesting that non-neutralizing Ab effects were critical. These effects could be mediated by either the Fab portion of the Ab which binds to antigens on the surface of the virus or virus-infected cell

and/or by the Fc portion of the Ab which binds to Fc receptors (FcRs) after the Fab fragment binds to its antigen.

Anti-viral activities mediated by the Fab fragment of antibodies.—Neutralization of virus infectivity is the most frequently measured anti-viral activity, resulting as a function of the attachment of Abs to virions. However, several other phenomena belong to this category of anti-viral functions and appear to play a critical role *in vivo* (57). These include:

a. *Virus Aggregation*. Abs can bind to virions; when they do, they can aggregate viruses, enhancing their destruction via phagocytosis. It has been shown that there is a clear association between virus aggregation and virus phagocytosis (58), and this may play a role in reducing the virus inoculum upon exposure to the virus, resulting in a reduced risk of infection. Similarly, this mechanism may assist in the clearance of circulating virus, which, perhaps as a result, has a half-life in circulation of only approximately 0.3 days (59). Monoclonal IgG and dimeric IgA Abs, as well as polyclonal purified serum IgA from RV144 participants, have been shown to aggregate HIV virions, and the specificities of the Abs used to do so include mAbs to various epitopes of both gp120 and gp41 (60).

b. *Virus Capture*. This *in vitro* assay has been used to demonstrate that the RV144 vaccine-elicited gp120-specific Abs of multiple specificities (V3, V2, and C1) can bind to virions (61). These studies were extended to show that C1- and V2-specific mAbs derived from vaccinees acted in synergy to capture virions (46).

c. *Inhibition of virus binding to cell-surface α4β7*: It was shown in 2008 that a tripeptide in the V2 loop of gp120 (at AA 179–181) constitutes a motif that mimics structures presented by the natural ligands of the α4β7 integrin, a gut-homing receptor, and that the HIV-1 envelope protein gp120 bound to an activated form of α4β7 (62). In a recent follow-up to the initial findings, the V2 domain of gp120 was shown to preferentially engage extended forms of α4β7 in a cation-sensitive manner. A 15-mer V2-derived peptide (AA 168–181) can bind to α4β7, and V2p-specific mAbs derived from vaccinated and infected subjects recognize this peptide and block the V2/α4β7 interaction (63). Other labs have reproduced and extended these findings (64) and have shown that purified IgG from some uninfected RV144 vaccinees can also inhibit the V2/α4β7 interaction. These data suggest that anti-V2 Abs may play a role *in vivo*, blocking the gp120/α4β7 interaction and thus preventing HIV acquisition and/or controlling early targeting of the gut lymphoid tissues by the virus.

Fc-dependent effector functions.—Many Abs result in anti-viral effects due to their ability to bind to infected cells and/or virions, leading to conformational changes in the Fc fragment which allow it to bind to FcRs on the surface of various cell types such as T cells, monocyte/macrophages, polymorphonuclear granulocytes, dendritic cells, etc. These Abs include both bnAbs and Abs that are poor or non-neutralizers, can be specific for various regions of the gp120 and gp41 Env proteins (Figure 3 and (19, 30, 40, 46, 65–71)), and can bind to the Env trimer in its different states (closed, partially open, or fully open (16). The

Fc/FcR interaction initiates anti-viral activities that include Ab-dependent cellular phagocytosis (ADCP) and Ab-dependent cellular cytotoxicity (2, 4, 46, 72–74) as well as complement virolysis (38, 75–77). Many of these mechanisms have been associated with reduced risk of infection. For example, ADCP has been associated with reduced HIV infection risk in humans (38, 78) and with SIV infection in NHPs (12), and Ab-dependent complement activation and deposition (79, 80) as well as Ab-dependent cell-mediated viral inhibition have been shown to contribute to control of SIV and SHIV (81–84).

CONCLUSIONS

The first and only independent correlate of reduced risk of HIV infection in humans was identified by studies of participants in the RV144 clinical vaccine trial: a robust Ab response to the V1V2 region of the virus gp120 Env glycoprotein. Subsequent to this observation, several active and passive immunization studies in NHPs identified the presence and level of V2 Abs as correlates of protection from SIV and SHIV infections. Currently, 11 vaccine studies in humans and NHPs (summarized in Table 1) support the role of V1V2-specific Abs in protection. In each case, the Abs involved displayed little or no neutralizing activity but mediated other anti-viral activities. Protection was documented against viruses heterologous to the strains used in the vaccines. These studies suggest a new paradigm for vaccine development: protection from and/or control of infection can be achieved with Abs that: (i) are induced by existing vaccine constructs, (ii) are effective against heterologous viruses, (iii) do not display broad and potent neutralizing activity, and (iv) mediate a variety of non-neutralizing Fab- and Fc-mediated anti-viral activities.

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Conflicts of interest. None

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KEY POINTS

- V2-specific non-neutralizing Abs are involved in the control of and/or protection from HIV, SIV and SHIV.
- The V2 Abs that correlate with protection after active or passive immunization are specific for the continuous epitope in the C-strand of V2 and/or for a discontinuous epitope that includes residues in V1 and V2, including the tripeptide α4β7 integrin binding motif in V2 (V2p and V2i Abs, respectively).
- Fc-mediated anti-viral Ab activities play an important role in control of and/or protection from HIV, SIV, and SHIV infection.

Type	mAb example	Epitope
V2q	PG9	trimer preferring
V2qt	PGT145	trimer-dependent
V2i	830A	discontinuous regions of V1 and V2
V2p	CH58	α-helix in V2 C-strand

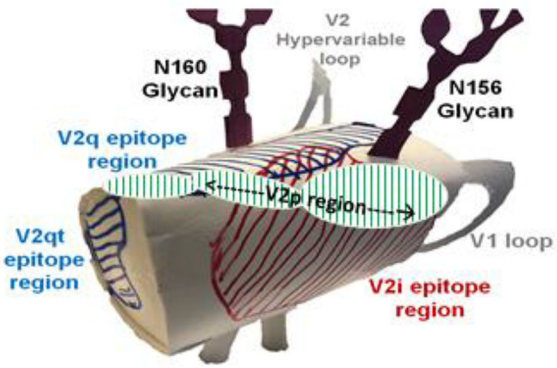

Figure 1.

Diagram of the position of the four epitope classes in the V1V2 region (V2p, V2i, V2q and V2qt), and examples of mAbs that target each of these epitopes.

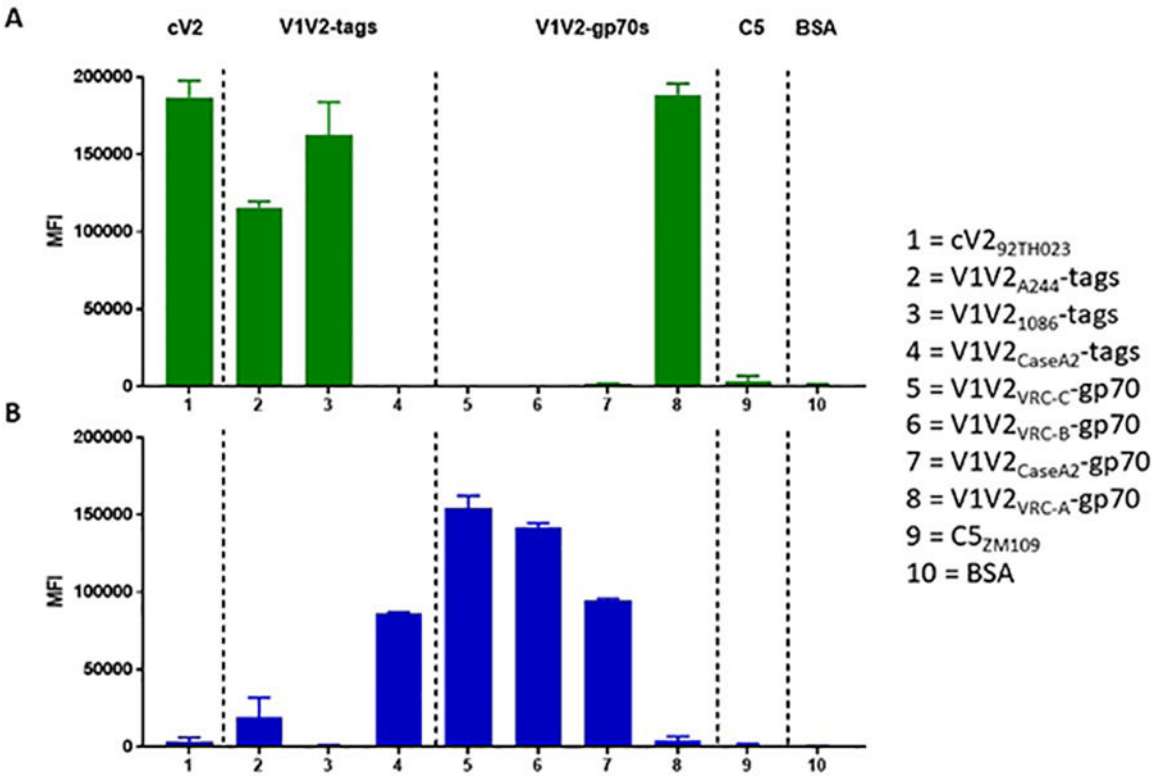

Figure. 2.

Luminex reactivity of V2p mAb 8490 (A) and V2i mAb 697–30D (B) vs. cyclic V2 peptide (column 1), V1V2-tags (columns 2–4), V1V2-gp70 fusion proteins (columns 5–8), C5 peptide (column 9) and BSA (column 10). The negative control is shown at right.

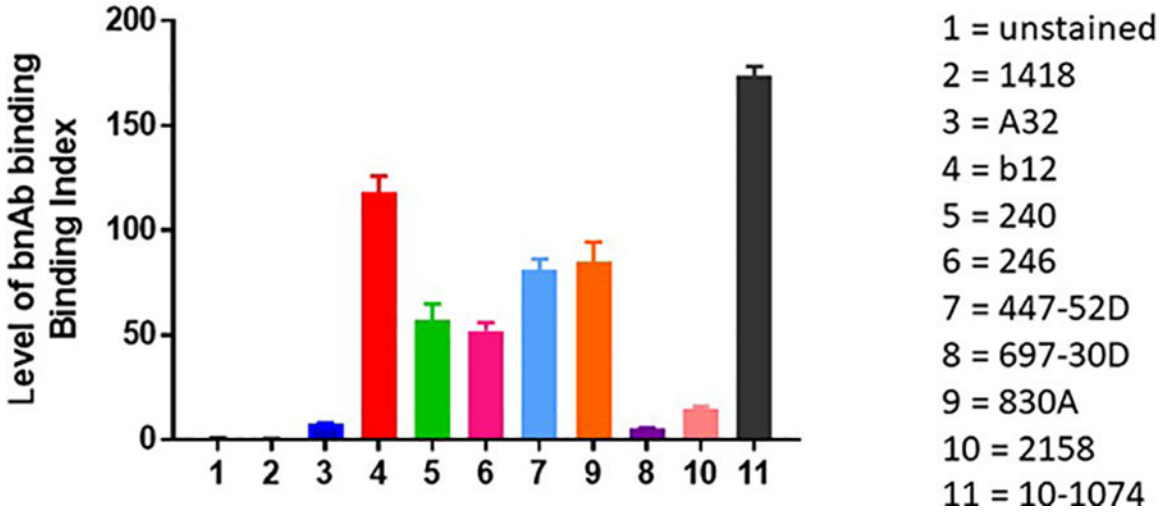

Figure 3.

Level of binding of mAbs to native-like Env. Results shown are for binding of mAbs to tetherin^{hi} Jurkat cells nucleofected with an mCherry+ NL4–3 reporter construct as described by Alvarez et al (71). Monoclonal Abs used (and the epitope for which they are specific) include: human anti-parvovirus mAb (1418), A32 (anti-C1), b12 (CD4bs), 240 & 246 (anti-gp41, cluster I), 447–52D (V3 crown), 697–30D (V2i), 830A (V2i), 2158 (V2i), and 10–1074 (V3-glycan).

Table 1.

Studies showing statistically significant correlation of V2-specific antibodies that confer protection from and/or control of HIV, SIV and SHIV

Year	Protection and/or control of	Correlation with Abs specific for	Immunization	Reference
2012	HIV	V2i	Active	Haynes et al (32)
	SIV_{mac251}	V2p	Active	Barouch et al (48)
2013	HIV	V2p	Active	Gottardo et al (43)
	SIV_{mac251}	V2p	Active	Pegu et al (51)
2014	SIV_{mac251}	V2p	Active	Gordon et al (52)
2015	SIV_{E660}	V2p	Active	Roederer et al (49)
2016	SIV_{mac251}	V2p	Active	Vaccari et al (50)
2018	$SHIV_{BaL}$	V2i	Passive	Hessell et al (56)
	SIV_{smE66}	V2p	Active	Singh et al (53)
	$SHIV_{BaL}$	V2	Active	Hessell et al (54)
	$SHIV_{BaL}$	V2p	Active	Weiss et al (55)