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## The role of Fc Receptors in HIV Prevention and Therapy

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### Abstract

Over the past decade, a wealth of experimental evidence has accumulated supporting the importance of Fc receptor (FcR) ligation in antibody-mediated pathology and protection in many disease states. Here we present the diverse evidence base that has accumulated as to the importance of antibody effector functions in the setting of HIV prevention and therapy, including clinical correlates, genetic associations, viral evasion strategies, and a rapidly growing number of compelling animal model experiments. Collectively, this work identifies antibody interactions with FcR as important to both therapeutic and prophylactic strategies involving both passive and active immunity. These findings mirror those in other fields as investigators continue to work toward identifying the right antibodies and the right effectors to be present at the right sites at the right time.

### Introduction

Over the past several years, there has been significant effort in HIV research to analyze the natural antibody response to infection in order to enable the development of effective strategies for infection prevention and post-exposure eradication. These studies have led to the discovery of a number of highly potent broadly neutralizing antibodies whose effectiveness as potential therapeutics does not derive from virus strain coverage and neutralization potency alone(1). Evidence from natural infection, vaccination and antibody passive transfer studies in humans, non-human primates (NHP), and mouse models have each provided evidence of the critical roles antibody Fc receptors (FcRs) can play in infection prevention and post-exposure therapy. These receptors drive effector functions such as antibody-dependent cellular cytotoxicity (ADCC), virus inhibition (ADCVI), phagocytosis (ADCP), antigen presentation, B-cell activation, complement dependent cytotoxicity (CDC) and dictate antibody half-life and biodistribution in vivo. This review will highlight some of the recent studies performed to elucidate the role that FcRs play in the context of HIV with the goal to inform and promote further exploration of vaccine and therapeutic strategies designed to exploit FcR-dependent mechanisms for improved clinical outcomes.

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A landmark passive transfer study in rhesus macaque revealed that engagement of Fc $\gamma$ R<sub>s</sub> contributes to the protective activity of broadly neutralizing antibodies in prevention of HIV infection (1, 2). In humans, Fc $\gamma$ R receptors Fc $\gamma$ RI, Fc $\gamma$ RIIa, Fc $\gamma$ RIIb, Fc $\gamma$ RIIc, Fc $\gamma$ RIIIa and Fc $\gamma$ RIIIb are widely expressed on immune cells including macrophages, neutrophils, natural killer (NK) cells, eosinophils, basophils, and dendritic cells. These cell types have varying receptor expression profiles and engage in different effector functions such as ADCVI or ADCC against cells with viruses entering or budding and phagocytosis of Ab-virus immune complexes or infected cells, among others. Functional relationships between receptors and cell types are complex as differential engagement between activating and inhibitory Fc $\gamma$ R<sub>s</sub> modulates cellular effector function(3). Receptors can also play additional roles in antigen presentation(4), B-cell inhibition and activation(5) and potentially HIV neutralization or infection inhibition on susceptible cells(6, 7).

The classical Fc $\gamma$ R consist of a family of immunoglobulin superfamily cell surface receptors with specificity to IgG, among which affinity, IgG subclass specificity, expression, signaling mechanisms, and ligation outcomes differ (Figure 1). Briefly, Fc $\gamma$ RI is an activating receptor comprising of an  $\alpha$ -chain with an intracellular domain which forms a complex with the signal transducing common FcR $\gamma$ -chain dimer. Fc $\gamma$ RIIa is an activating receptor with an intracellular immunoreceptor tyrosine-based activating motif (ITAM). A soluble form of Fc $\gamma$ RIIa is found in serum and is either shed from the surface of cells or expressed in a truncated form missing the transmembrane domain secreted from Langerhans cells(8). Fc $\gamma$ RIIb is an inhibitory receptor comprising an intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM). Fc $\gamma$ RIIc is an activating receptor with the extracellular domain identical to Fc $\gamma$ RIIb and an intracellular ITAM domain identical to Fc $\gamma$ RIIa. Fc $\gamma$ RIIIa is an activating receptor reliant on the common FcR $\gamma$ -chain for signal transduction. Fc $\gamma$ RIIIb is exclusively expressed on neutrophils and is tethered to the cell membrane through a glycosylphosphatidylinositol (GPI) anchor; despite lacking an intracellular domain, Fc $\gamma$ RIIIb is capable of triggering release of oxidative species(9), driving phagocytosis(10), as well as impairing Fc $\gamma$ RIIa-driven ADCC(11). Soluble Fc $\gamma$ RIII is also found in serum by shedding from macrophages, natural killer cells, some T cells and neutrophils, and has been found to increase early in HIV infection and decrease in patients with late stage AIDS(12). Soluble Fc $\gamma$ RIII has also been shown to inhibit HIV infection of monocytes/macrophates by blocking CR3(13). The biophysical characteristics of Fc $\gamma$ R and their allotypic variants, which will be discussed later, are summarized in Figure 1 (adapted from(14)).

Collectively, these Fc receptors underlie the landscape of antibody-mediated anti-viral effector activity. Here we describe the experimental evidence base as to the role of FcR in HIV vaccination, infection, progression, and therapy. Beyond classical Fc $\gamma$ R, a few recent studies have demonstrated the value of more inclusive examination of the role of diverse FcR in prevention and therapy. We close by discussing recent findings relating the efficacy of antibody-based prevention with interactions with the neonatal Fc receptor (FcRn) responsible for IgG recycling and mucosal delivery; the potential role of IgA and Fc $\alpha$ R<sub>s</sub> in protection from infection, and the growing potential for the use of novel therapeutic strategies used vectored antibody delivery to prevent or treat HIV infection.

## Correlates associated with FcR-mediated effector function

Correlates of FcR-mediated effector function have been increasingly prevalent in the HIV literature in recent years, both in the setting of natural infection and vaccine-induced immunity. Collectively, evidence from multiple human vaccine trials and a number of NHP studies have identified a role for ligation of FcR in protection from infection.

### Human vaccine trials

The most well-studied example of the importance of FcR function in vaccination is the modestly protective RV144 vaccine trial, for which a binding antibody response against the V1/V2 region of the viral envelope was shown to correlate with reduced risk of infection(15), and modulation in breakthrough virus sequence characteristics(16). Conversely, IgA titer against the virus was shown to correlate with an increased risk of infection; whereas higher levels of ADCC activity in low IgA responders was shown to be associated with lower risk of infection(15). These findings imply either a competitive mechanism of protection: whereby IgA, with different capacity to engage FcRs, can actually block a more productive IgG response(17); or a more broadly qualitative mechanism of protection: whereby qualitative characteristics of the overall humoral response dictate the degree of protection. In both cases, the isotype signals observed point toward a relevance of FcR-mediated activities. These findings were additionally strengthened last year with the finding that envelope-specific IgG3 responses, associated with polyfunctional effector activity, were also a correlate of reduced risk of infection(18, 19).

Additional evidence for the importance of FcR-mediated effector function is provided by several earlier trials. Though non-protective overall, in the Vax004 trial ADCC activity was shown to correlate inversely with infection risk(20). In the related Vax003 trial the envelope specific response was shown to have a strong IgG4 bias, associated with reduced antibody effector function(18). These findings support the RV144 antibody effector quality hypothesis, in that the presence of poorly functional Ig, whether IgA or IgG4, seems to reduce the ability of more functional IgG1/3 responses to provide protection from infection. In a modeling study, a negative impact of HIV-specific IgG2 and IgG4 responses could be observed in predictions of ADCC and ADCP activities(21), and this hypothesis was further strengthened by depletion studies in which removal of the IgG4 fraction caused an increase in the effector activity of the remaining antibody pool(18).

### Nonhuman primate studies

Several non-human primate vaccine regimens with varying levels of protective efficacy have suggested that Fc-mediated effector function plays a role in either reduced risk of infection or lower viral load post infection (summarized in (22)). These studies have evaluated the effect of FcR-dependent antibody function against whole envelope, mosaic envelope and specific envelope conformations such as the CD4-induced state. In addition, these outcomes have been shown both in the context of subunit protein and adenovirus vector derived antibody responses against both SIV and SHIV.

Antibody effector correlates such as ADCC have long been associated with reduced viremia in the rhesus macaque model(23). In this study an adenoviral vector prime was followed by a homologous boost with SIV gp120 protein. While the authors were unable to demonstrate protection against the homologous SIVmac239 challenge strain, they showed strong ADCC responses, which correlated with reduced acute viral load. A more recent trial with an adenoviral vector expressed mosaic Env/Gag/Pol antigen showed significant reduction in per-exposure acquisition risk upon multiple rectal challenges against a similar neutralization resistant challenge model (SHIV-SF162-P3)(24). In this case, the protective response was entirely against the Env portion of the antigen, as the challenge strain contained SIV Gag/Pol with low homology to the HIV antigens in the mosaic being tested. A number of neutralizing and non-neutralizing Ab measurements correlated with protection, including binding titer, neutralizing titer, ADCP and complement deposition. A further interesting study was published this year using CD4-induced gp120 as an immunogen in rhesus macaques, in which protection correlated with antibody titer and ADCC activity, but not neutralization, and was inversely correlated with high vaccine elicited T-cell responses(25). This antigen induced primarily non-neutralizing but ADCC-capable antibodies, which showed significant protection against multiple low dose SHIV and SIV challenges. Addition of tetanus toxoid to the vaccination regime increased T-cell responses but decreased the level of protection seen. This result is hypothesized to occur similarly to the increase in infectivity found in the Step trials, where HIV-specific T-cell responses are thought to have increased susceptibility to infection(26). Intriguingly, a different protective vaccine study in rhesus macaques suggested that protection may have been due to inhibited recruitment of CD4+ T cells to the site of infection based on immune complex binding to the inhibitory Fc $\gamma$ RIIb (27). It will be interesting to determine whether similar functional assessments in new or existing vaccine efficacy studies with established antibody correlates(28, 29) might complement and reinforce these associations with antibody functions.

## Passive transfer studies

### NHP models

Many passive transfer studies, in which neutralizing antibodies were administered intravenously in advance of viral challenge, have conclusively demonstrated that antibodies can protect from HIV infection. In a landmark study aimed at investigating the mechanism of this protection, the neutralizing antibody b12 was mutated to ablate interactions with FcR and or/complement. Despite equivalent neutralization potency and biodistribution, the silencing of antibody effector function caused half of the protective capacity to be lost(1). While a great deal of clinical data from human and NHP vaccine studies and from natural infection cohorts supports the significance of antibody effector function in impacting risk of infection, viral load, and progression(30), and points to the promise of rational optimization of effector function(14), an initial attempt to explore enhancing protection via differential binding to Fc $\gamma$ R receptors proved unsuccessful. Passive transfer of a nonfucosylated broadly neutralizing antibody with enhanced binding to Fc $\gamma$ RIIIa on NK cells did not augment protection from vaginal challenge(31). While many theories as to the lack of enhanced efficacy have been proposed, later studies have begun to point to a limited role of NK cells in controlling HIV transmission and containment during acute infection in the mucosa, in

favor or other effector cell types that may possess greater potential to impact mucosal transmission.

Following up on these studies, several attempts have been made to evaluate the ability of passively transferred antibodies to provide protection, with varying success. Highly functional, but non-neutralizing antibodies isolated from human HIV controllers were unable to protect macaques against high dose SHIV challenge(32). This experiment highlights some of the difficulties in achieving effective protection with passive transfer of human antibodies to macaques: no human antibody was found at the site of challenge (vaginal mucosa), and the authors were only able to transfer a single dose at a concentration estimated to be less than half that necessary for b12 to provide protection in this model. In another study SHIVIG, a polyclonal antibody mixture isolated from macaques with high neutralizing titers, was evaluated for protection against low-dose intra-rectal challenge. While lower viral titers were observed at peak viremia for the high IgG dose, a greater number of transmitted founder viruses were observed at lower doses, suggesting a potential danger of antibody dependent enhancement(33), which is also dependent on FcR interactions. In contrast, vaginal application of a non-neutralizing cocktail of 246-D and 4B3 with potent Fc-mediated *in vitro* virus inhibition did not confer protection from a vaginal SHIV challenge in rhesus macaques but did display a reduction plasma viral load likely through Fc $\gamma$ R-mediated effector function (34).

In other recent studies, passively transferred antibodies have exceeded expectations in remarkable ways. For example a cocktail of monoclonal neutralizing antibodies or even the single highly neutralizing monoclonal antibody PGT121 showed significant ability to suppress viremia in infected macaques(35), reinvigorating the notion that antibodies might be therapeutically useful. Similarly, an IgG1 Fc-mutant with increased FcRn affinity was shown to enhance protection against SHIV intra-rectal challenge(36), bolstering the possibility of using passively transferred antibodies as prevention. While FcRn binding does not directly enhance effector function it was shown to increase serum half-life threefold and enhance distribution to and persistence of antibody at the rectal mucosa. These recent findings highlight the diverse routes whereby FcR-mediated responses could help enhance antibody-based protection and therapy.

### Mouse models

The ability to increase protective efficacy by enhancing affinity to activating Fc $\gamma$ R has been compellingly demonstrated *in vivo* in protection using a humanized Fc $\gamma$ R mouse model for HIV(37). This mouse model exploits Fc $\gamma$ R chimeras consisting of human extracellular domains and mouse intracellular signaling domains(38). Conveniently the mice appear to recapitulate human Fc $\gamma$ R structural features, cellular expression patterns and effector functions. Using this model, the finding that neutralization alone is insufficient for the *in vivo* protection achieved by neutralizing antibodies has been generalized across many of the most potent and broad neutralizing antibodies(37). Further, a broadly neutralizing Fc point mutant with increased affinity to activating Fc $\gamma$ R displayed enhanced protection over wild type IgG.

Similarly, this model has been used to study the role of antibody-FcR interactions in the setting of antiviral antibody therapy. Here, antibodies were found to have strong potential in driving viral clearance based on their Fc domain and FcR-dependent ability to delay viral rebound following latent virus reactivation(39). In a subsequent study, this effect on delaying viral rebound was even more definitively linked to effective Fc $\gamma$ R ligation via use of Fc domain point mutants with alternatively enhanced or ablated Fc $\gamma$ R binding(37). These studies highlight that differential Fc $\gamma$ R engagement may be a key factor in therapeutic efficacy based on impacting effector function. Such studies potentially offer a tractable means to decipher the Fc $\gamma$ R and cell types involved in HIV protection and elimination.

### Human passive transfer studies

The setting of mother to child HIV transmission presents a passive transfer experiment conducted naturally, in which IgA and IgG antibodies are delivered through placental transport prior to birth and via ingestion of breast milk after birth. Although early studies did not find an association between infant or maternal ADCC and infection risk(40, 41), better clinical status and delayed progression was sometimes observed(42, 43). Two more recent studies that assessed ADCC activity in the setting of maternal to child transmission have found associations with reduced viral transmission or mortality. In the first(44), a trend toward increased ADCC activity among uninfected versus infected infants was observed, whereas no difference in IgG1, IgG3, or neutralization activities was observed. Survival was strongly impacted by ADCC activity, and an inverse trend between ADCC and set point viral load was noted. In another study, breast milk supernatant ADCC activity, but not HIV envelope-specific IgG titers were found to correlate inversely with transmission(45).

Rapid growth in our understanding of the role that passively transferred antibodies could play in HIV therapy or eradication is expected over the next few years on the heels of the discovery of more and more broad and potent neutralizing antibodies and results from pre-clinical models discussed above. Early studies with first generation neutralizing antibodies demonstrated that viral rebound could be delayed after treatment cessation (46), and could exert selective pressure on the sequence of circulating virus (47), but that antibodies did not appear to be strong candidates to supplant small molecule therapies. The more impressive suppression results observed recently in NHP and mouse models have triggered re-evaluation of the utility of antibodies in treatment.

In the first major experimental human passive transfer study to be published in many years, the broadly neutralizing antibody 3BNC117 was evaluated in HIV infected and uninfected subjects to determine pharmacokinetics, safety, and impact on viral load(48). Among HIV+ individuals, a mean decrease in viral load of 1.5 log<sub>10</sub> was observed. The impact of another antibody, KD-247, on viral RNA load was also recently reported, demonstrating an ability to reduce viral RNA by up to 1 log, with long-term viral suppression observed in one subject(49). These results, and the many broad and potent neutralizing antibodies now available for evaluation, point toward the possibility for use in combination in treatment and prevention strategies.



## Findings in natural infection

A number of studies point toward the relevance of antibody interactions with Fc $\gamma$ R in relation to disease progression (summarized in(30)). Briefly, in both humans and NHP, post-infection ADCC/ADCVI activity has been associated with viremic control and/or rate of disease progression(50–52), and conversely impaired ADCC and ADCP have been associated with progression(53, 54). In natural infection, Fc and Fab mediated HIV specific antibody activities appear to evolve independently(55), and *in vivo*, natural Fc $\gamma$ R affinity variants are generated by IgG subclass switching between IgG1, IgG2, IgG3, and IgG4 as well as the tuning the Fc glycan structures. Recent studies among infected subjects have indicated these subclass, glycan, and Fc $\gamma$ R-binding features can all impact the effector activity of HIV-specific antibodies (56–59), and further support the potential value of Fc tuning by antigenic cues in providing a new handle for modulating effector function by vaccination or in antibody therapy.

## Associations with Genetic Variation of Fc $\gamma$ R

Across the human population, a number of Fc $\gamma$ R genetic variants, including both copy number variants (CNV) as well as single nucleotide polymorphic variants (SNP) exist; this genetic diversity has been associated with functional consequences ranging from different cell surface expression levels, differing signaling capacity, to differential binding affinities to IgGs. Numerous relationships have been described relating Fc $\gamma$ R CNV and SNP variation in diverse clinical cohorts in the setting of monoclonal antibody therapy(60), autoimmunity(61), and susceptibility to and resulting outcomes from diverse infections(62–66). A summary of Fc $\gamma$ R alleles and their associations in HIV infection, vaccination and disease progression are summarized in Table 1.

### Fc $\gamma$ RII

While many studies have identified associations, the significance and possible mechanisms of these genetic variations on outcomes in HIV infection, disease progression, and vaccine responses remains unclear (recently reviewed in (74)). For example, among the two known allotypes of Fc $\gamma$ RIIa (H131, R131), the H131 allotype has higher affinity to IgG, particularly IgG2(75), and these allotypes have been implicated as factors in virus acquisition, disease progression and susceptibility to AIDS related infections. However, these associations are often somewhat contradictory and appear variable across different subject cohorts. For example HIV-infected men with the RR genotype had a faster rate of decline in CD4<sup>+</sup> T cells than HR or HH subjects, implying that enhanced IgG recognition may be protective(67). However, in the same study, a statistically significant difference in progression to AIDS in HH subjects was not observed, as HH subjects were more likely to be diagnosed with AIDS based on *Pneumocystis jiroveci* pneumonia, despite being less likely to be diagnosed with *P. jiroveci* subsequent to AIDS diagnosis. In contrast to this protective association with disease progression in adults, the HH genotype has been associated with increased perinatal HIV transmission(68). These apparent discrepancies are not easily resolved, and may arise due to the multiple and interacting factors that may impact clinical outcomes. For example, there are known associations between FcR genotype with

different levels responses across IgG subclasses. These subclass differences could then reinforce or undermine relationships between FcR genotype and effector cell activity. Evidence of these types of interactions can be found in a small therapeutic vaccine study, in which subjects with both the HH or HR genotype better able to recognize IgG2 and antigen-specific IgG2 production exhibited enhanced HIV control(69).

These examples highlight that interpreting associations observed between Fc $\gamma$ R allotypes and HIV outcomes can be perplexing. As a challenge in particular to the antibody-centric mechanisms presumed to be marked by genetic Fc $\gamma$ R associations, a recent comprehensive phenotypic analysis of 78,000 traits in 669 female twins revealed that Fc $\gamma$ RII polymorphisms are associated with numerous canonical traits on major immune cell subsets including T cells, B cells and dendritic cells(76). Associations were observed for CD27 expression on IgA<sup>+</sup> B-cells, IgG<sup>+</sup> B-cells, CD4<sup>+</sup> T-cells and CD8<sup>+</sup> T-cells, CD161 expression on CD4<sup>+</sup> T cells, expression of Fc $\gamma$ RII on CD1c<sup>+</sup> myeloid dendritic cells (mDC) and inflammatory myeloid dendritic cells (iMDC). Interestingly, CD27 is capable of inducing apoptosis(77) and high expression is associated with long-term survival of CD8<sup>+</sup> T cells in HIV-infected patients(78) while a loss of CD27<sup>+</sup> B cells is associated with HIV infection and inversely correlated with CD70<sup>+</sup> (CD27 ligand) T cells(79). Additionally, CD161<sup>+</sup> CD4<sup>+</sup> T cells are significantly reduce during HIV infection and have recently been identified as a precursor to gut homing Th17 T cells which are profoundly depleted potentially leading to overall impairment of mucosal immunity during infection(80). Evidently, Fc $\gamma$ RIIa allotypes have profound associations beyond their impact on IgG subclass specificity and further work must be performed to elucidate the mechanisms behind the associations with T cell, B cells and dendritic cells and the effect on infection susceptibility, disease progression, and outcomes of vaccination.

Fc $\gamma$ RIIb has no known allotypic variation in the extracellular domain, however it does have two known allotypes, I232 or T232, in the transmembrane helix. The T232 allotype is unable to activate intracellular inhibitory receptors due to T232 exclusion from sphingolipid rafts(81). The resulting lack of B cell receptor signal inhibition leads to unopposed pro-inflammatory signaling linked to systemic lupus erythematosus (SLE)(82). Interestingly, autoantigens associated with SLE have been identified to have sequence homology with HIV retroviral machinery such as gag and/or env as well as confirmed antibody cross-reactivity(83). Additionally, a broadly neutralizing antibody was isolated from an SLE/HIV patient was cross-reactive with both SLE associated dsDNA and the CD4 binding site of gp120(84), resulting in increasing interest in understanding how host tolerance mechanisms may impact on bnAb development(85). As more patients are identified that have concomitant autoimmunity and HIV it would be interesting to genotype Fc $\gamma$ RIIb allotypes to parse any associations with disease susceptibility and progression.

In 20% of healthy individuals(86, 87), Fc $\gamma$ RIIc is expressed on NK cells and B cells due to an open reading frame (ORF) allele. On NK cells it is capable of eliciting ADCC independent of Fc $\gamma$ RIIIa(86) and on B cells it can enhance B cell activation(5). Additionally a nonclassical ORF allele in Fc $\gamma$ RIIc drives expression of full length Fc $\gamma$ RIIb on NK cells, and is capable of inhibiting Fc $\gamma$ RIIIa driven ADCC(87). Intriguingly, an Fc $\gamma$ RIIc SNP resulting in a premature stop codon was recently associated with reduced risk of infection in



the RV144 vaccine trial where efficacy varied from an estimated 15% to 91% across polymorphic vaccinees(73). Given the limited information about Fc $\gamma$ RIIc expression and activity, the functional association of this SNP remains undetermined.

### **Fc $\gamma$ RIII**

Fc $\gamma$ RIIIa has two allotypes, V158 or F158, where V158 has higher affinity to all IgG subclasses than F158(88). Like Fc $\gamma$ RIIa, clinical associations of the Fc $\gamma$ RIIIa allotypes in the context of HIV are not entirely clear. One study concluded that V/F genotypes were not associated with differences in HIV progression(67); however another study indicated the V and VV alleles were risk factors for both HIV infection and progression, respectively(70). This result is also consistent with the Vax004 trial, in which subjects with the VV allele had a higher risk of HIV infection than subjects with either VF or FF alleles(71). In contrast, in the Step trial, no Fc $\gamma$ RIIIa allotype alone impacted likelihood of infection(72). Collectively, these findings are somewhat surprising, and counter to run the simplest expectations one might form based on studies in antibody therapy of numerous cancer types where the high affinity V allele is associated with better outcomes.

Fc $\gamma$ RIIIb has three known allotypes NA1, NA2 and SH where allotypic differences in the population have been correlated to autoimmunity such as SLE(89) or susceptibility to pathogenic infections such as malaria(9). Few studies have evaluated Fc $\gamma$ RIIIb allotypes in the context of HIV, however one study indicated that a CNV allele in Fc $\gamma$ RIIIb had an effect where a deletion was more frequent in HIV-tuberculosis co-infection(90). Despite Fc $\gamma$ RIIIb's ability to modulate neutrophil effector function, sufficient evidence has not accumulated to define clear roles for Fc $\gamma$ RIIIb in HIV protection or infection.

Overall, the variation in associations observed in these studies highlight the context dependence of allelic effects across different populations, different age groups, and different disease states. Different Fc $\gamma$ R genotypes may be optimal pre-infection, post-infection, or in the setting of vaccination based on their widespread and pleiotropic effects. The impact of Fc $\gamma$ R genotype on multiple key immune phenotypes, including variance in their ability to interact with acute phase proteins, and their linkage disequilibrium confound analysis and interpretation. Clearly, caution must be taken when attempting to glean generalizable trends, particularly from small studies. Overall, there appears to be limited evidence to support simple interpretations of these associations as directly mechanistically associated with variation in effector activity due to differential interactions with IgG. Hopefully, as more human passive transfer experiments are conducted, the role of Fc $\gamma$ R allotypic variation in modulating at least antibody-mediated protection will become clearer.

### **Evidence of virologic evasion**

Evidence as to the importance of FcR-mediated anti-viral activities can be found in viral evasion strategies. Beyond the well-known antigenic variation strategies HIV employs based on its low fidelity polymerase, which serves to remove the link between Ab and virus upstream of Fc-dependent activities, several viral genes have been characterized as having roles in modulating downstream antibody-FcR biology. For example, HIV negative factor

(Nef) has been reported to influence class switching in trans in B cells, resulting in inhibition of class switching to IgA or IgG (91, 92).

Similarly, the Viral protein U (Vpu) is thought to act as a virulence factor by interfering with the host response to viral infection in a number of ways. Recently, Vpu was shown to directly interact with and antagonize the interferon-induced host protein tetherin (BST-2) (93), whose native function is to inhibit release of enveloped viruses by securing budding virions to the cell surface. When tetherin expression was knocked down via RNAi, infected cells were resistant to ADCC(94). Conversely, when tetherin and CD4 expression were increased via interferon treatment, cells were sensitized to ADCC. Perhaps most compellingly, when specific mutations were made in Vpu that impaired the interaction with tetherin, cells were likewise sensitized to antibody-mediated cytolysis. A final aspect of immune evasion by Vpu may be found in its role in combination with Nef in downregulating CD4, which has been found to increase exposure of CD4-induced conformations of the HIV envelope protein, thought by some to be particularly relevant to ADCC(95, 96). Support for this notion was recently found in the ability of small molecule CD4 mimetics to also sensitize HIV-infected cells to anti-viral antibodies(97).

Lastly, HIV possesses extensive strategies for the evasion of complement-mediated lysis, while at the same time maintaining recognition by numerous complement receptors and several other lectins that may facilitate establishment of reservoirs of viral particles (summarized in(98, 99)). A long-standing body of literature describes modulation of lysis by means of complement regulatory factors including Decay Accelerating Factor (CD55) and membrane inhibitor of reactive lysis (MIRL, CD59)(100), and interactions with complement factor H (fH) in serum(101). More recent work has identified a role of complement opsonization in reducing antiviral inflammatory responses in immature dendritic cells(102). It is interesting to consider the possibility that the lack of dependence of b12-mediated protection from infection on complement may be partially dependent on factors such as these.

## The role of viral recognition in antibody activity

Diverse envelope protein epitopes have been identified that permit ADCC including sites on gp41 such as the membrane proximal external region (MPER) or sites on gp120 such as glycosylation sites, the CD4 binding site, the V2/V3 loops and CD4-induced epitopes (CD4i) capable of binding envelope upon a conformational change due to gp120 binding to CD4 (recently reviewed(103)). However, the ability for an antibody to bind an epitope alone does not alone guarantee efficient engagement of FcRs. Recent studies in HIV and other infectious diseases as well as oncology have revealed the interplay between epitope location and structure, the valency of antibody epitope binding, Fc orientation and accessibility towards FcR as well as IgG avidity (104) and resulting immune complex size(105) that can dramatically impact FcR mediated effector function.

CD4i epitopes are of particular interest in HIV given the antibodies they produce are prevalent in patients undergoing HAART treatment during acute infection (106), dominant determinants of serum-mediated ADCC in chronically infected individuals(96) as well as

highly prevalent among RV144 vaccinees(107), highlighting the strong immunogenicity of CD4i complexes, their involvement as an effective ADCC mediator and their potential value as vaccine immunogens. A recent study comparing two CD4i antibodies has raised additional considerations for epitope targeting and immunogen design where antibodies 2.2c and N5-i5 had similar monovalent affinities however their bivalent affinities towards antigen on the target cell surface differed 18-fold due to differential ability to crosslink antigen. Additionally, a VH-VL domain swap which reoriented the antibody Fc domain altered ADCC activity by an order of magnitude (108). Monoclonal antibody studies such as this highlight the importance of antibody valency towards antigen as well as the criticality of antigen binding geometry based on impacting Fc orientation and accessibility to Fc $\gamma$ R.

Effector function depends on efficient opsonization, and antibody crosslinking of HIV antigen on a target cell surface has been previously demonstrated to enhance neutralization potency(109). However, isolation of naturally occurring antibodies that can crosslink antigen on free HIV virus has been a challenge. Bivalent and highly avid antibody binding to free virus has been previously demonstrated for icosahedral rhinovirus(110), poliovirus(111), and more recently for dengue virus (112, 113). A major distinction from most viruses is that an HIV virus contains as few as 7–14 envelope spike protein trimers on its surface(114) and it has been proposed that the virus has evolved to sparsely display trimers to evade bivalent antibody interactions, amplifying the challenge HIV imposes on the humoral immune system's ability to develop potent neutralizing antibodies(115). Additionally, because efficient ligation of most Fc $\gamma$ R requires avid interactions, one could also speculate that this scarcity of trimer targets additionally increases resistance to Fc mediated effector functions which requires immune complex formation. Analysis of cryo-electron tomography data revealed the most frequent nearest neighbor distance between trimer spikes was 15 nm, within the paratope to paratope reach of a typical antibody(116), resulting from a clustered trimer formation which was shown to be necessary for efficient viral entry(117–119). If it is indeed necessary for trimers to cluster for efficient viral entry, then the viruses most critical to block and clear will opportunistically have a skewed trimer distribution more amenable to bivalent antibody binding, and avid opsonization.

A previous study examining antibody architectures with altered distances between variable regions indicated binding one antibody between two spikes (inter-spike) is possible for CD4 binding site antibodies like b12 but unlikely for gp41-specific antibodies like 4E10; increasing distance and flexibility between variable regions was associated with enhanced neutralization, suggesting both a lack of trimer mobility, and the importance of an avid interaction(120). Additionally, a recent study using a “molecular ruler” technique based on linking two Fabs by DNA showed intra-spike crosslinking strongly potentiated virus neutralization. There is additional support that avid Fab binding is advantageous from studying natural antibodies, where it has been previously shown that divalent Fab'<sub>2</sub> possess superior neutralization activity relative to monovalent Fab(121). Interestingly, a subclass-dependent difference in Fab'<sub>2</sub> neutralization was also noted in this study. HIVIG-derived divalent Fab'<sub>2</sub> from the IgG3 fraction provided better neutralization than either IgG1 or IgG2 Fab'<sub>2</sub>, despite equivalent performance as a monovalent Fab. Interestingly, IgG3 antibodies have been characterized to have increased conformational flexibility relative to other

subclasses(122), supporting the notion that better bivalent recognition may underlie the enhanced activity of this subclass.

The development of intra-spike bivalent binding antibodies is thought to be uncommon, however carbohydrate constellations on HIV trimer provide a unique opportunity. For instance 2G12 binds di-mannose residues effectively due to a VH-VL domain exchange leading to bivalent binding and potent neutralization(123). Additionally a naturally dimeric form of 2G12 that contains 2 Fc regions has also been shown to have improved neutralization potency and ADCC(124) highlighting the powerful effector function potentiation dimeric IgG binding can elicit. Further evidence as to the importance of avidity and epitope-dependent exposure of the Fc to effector activity can be found in a 2G12 isotype-switch experiment. 2G12 and gp41 targeting 2F5 antibodies were isotype switched to polymeric IgM, resulting in an increase in complement activation for 2G12 but a reduction for 2F5(125). This study highlights how the nature of how an antibody binds to its epitope can determine the inducibility of complement due to Fc clustering, orientation and steric hinderance. Interestingly, it was recently discovered that IgGs are capable of forming noncovalent hexamers when binding antigen on cells, and this higher order hexameric Fc structure enables avid engagement with C1q(126), depending on the presence or absence of C-terminal lysines(127). This finding corroborates previous speculation that antibodies binding at the surface of the cell may participate in Fc:Fc interactions(128) and may also explain notable modulation of complement deposition among anti-CD20 antibodies which target different epitopes based on variance in the ability to arrange Fc units for optimal engagement of C1q(129, 130).

## Role of FcRn in HIV

The neonatal Fc receptor (FcRn) binds IgG in a pH dependent manner and modulates IgG half-life as well as biodistribution *in vivo*. A recent study in rhesus macaques using an IgG1 Fc mutant with increased pH sensitive affinity to FcRn improved transcytosis of IgG across cellular monolayers *in vitro*, increased serum half-life three fold, increased distribution and persistence of IgG in the rectum, and most importantly, significantly improved protection from SHIV intrarectal challenges(36). This study points to several new and important considerations: first, rather than exclusively serving as a means to decrease dose or extend the dosing interval for a mAb, enhanced FcRn recognition can provide specific transport to relevant sites of viral exposure. This study also raises an important consideration regarding the IgG3 correlate observed in the RV144 trial(19). There are numerous IgG3 allotypes in the human population, two of which (G3m15, G3m16), exhibit FcRn binding and plasma half-life similar to that of IgG1(131, 132), rather than the greatly reduced half-life of most IgG3 allotypes. Thus, depending on allotype, naturally induced or recombinant IgG3 serum half-life and compartmental distribution could be dramatically impacted. It is interesting to note that the RV144 trial occurred in Thailand and the G3m15 and G3m16 allotypes, uncommon in Europe (~1%), are quite prevalent in Asia (10–50%)(133). In passive immunization studies, additional exploration of the effects of enhanced binding to FcRn as well as Fc $\gamma$ Rs can be achieved by combining antibody Fc amino acid mutations or glycosylation engineering strategies(134, 135) to maximize both biodistribution and anti-viral bioactivity.

Beyond half-life and biodistribution, FcRn plays novel roles in IgG mediated phagocytosis(136) and immune complex processing. Recent *in vitro* data suggests FcRn enhances opsonized HIV transcytosis across epithelial layers(137, 138); however, it has also been described to divert immune complexes to lysosomes for antigen processing(139). In dendritic cells, FcRn regulates IgG immune complex processing into peptides compatible with MHC I and II and enables activation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells linking the humoral and cellular branches of the adaptive immune response (140). Further research into the potential role of FcRn in HIV dissemination and antigen processing could enable therapeutic strategies to better exploit these properties.

## Role of IgA and its receptors in HIV

IgA is the most abundant antibody in the mucosa and can drive effector functions such as phagocytosis, ADCC, and release of cytokines and activated oxygen species through FcαR present on neutrophils, monocytes, eosinophils and some macrophages and dendritic cells(141). Dimeric IgA (dIgA) attachment to the polymeric Ig receptor (pIgR) enables transport to mucosal surfaces and results in release of secretory IgA (sIgA). Although their biological relevance in HIV is unknown, additional receptors for IgA have been reported in humans such as Fcα/μR, which binds both IgA and IgM, and the transferrin receptor, which is selective for monomeric IgA1(142). Overall, IgA is potentially an appealing candidate for HIV protection given its relevant localization in the mucosa as well as its potential in both virus neutralization and effector function. A number of studies have characterized the distinguishing features of the IgA subclasses, their compartmentalization and their potential relation to HIV protection as well as effector function relative to IgG.

Thus far, however, data has not converged on the possible role of IgA in HIV(143). The recent RV144 trial conferred 31% protective efficacy; however, HIV-specific IgA levels were higher in vaccine recipients who became infected, implying a negative role for IgA in vaccine-mediated protection (15). Whether this effect was a marker of other differences in subject immune responses, or a direct indicator of mechanisms of protection is unclear. A follow up study aimed at addressing this correlation found that IgA /IgG ratios were higher among infected subjects, that vaccine-induced IgA could block IgG mAb mediated ADCC, and that an IgA mAb isolated from a vaccinee could inhibit the ADCC activity of vaccine-induced IgG responses(17).

This human vaccine trial data conflicts with results from IgA passive transfer experiments and some vaccine studies in animal models. For example, to evaluate the neutralizing abilities of IgA, an intrarectal antibody administration and virus challenge study in infant rhesus macaques using dIgA1, dIgA2 and IgG1 with the same neutralizing Fv was conducted. In this study dIgA1 demonstrated the best protective capacity, which was associated with higher virion capture and inhibition of virus transcytosis(144). Interestingly, dimeric IgA has previously been shown to elicit more potent FcR mediated effector functions over both monomeric IgA and IgG1 in cell based assays(145). While the result of this IgG/A *in vivo* comparative experiment was surprising, it is confounded by potential differences associated with intrarectal IgG/A delivery, distribution, or persistence, and potential differences in effector populations in infant animals, as much as it may be driven

by differences in the protective capacity of isotypes. Thus, to more directly assess whether IgA and IgG responses might either compete or constructively reinforce with each other, a follow up study combined intravenous IgG1 with mucosal administration of dIgA1. The combination demonstrated superior protection to both IgG1 alone and dIgA alone, indicating that an immune response with both serum IgG1 and mucosal IgA1, even to the same epitope, could provide enhanced protection from SHIV(146).

Similar support for a protective role for IgA exists in a mucosal vaccination study in rhesus macaques in which sIgA titers in the rectum correlated with delayed acquisition in addition to anti-envelope antibody avidity, and ADCC titers correlated with the number of exposures required for infection(147). In humans, mucosal HIV-specific IgA responses have been observed among exposed but uninfected subjects at multiple sites of transmission(148–151). While there is long-standing evidence that HIV-specific IgA can mediate ADCC(152), recent attention has been paid to the potential ability of IgA to aggregate and trap virions at mucosal sites(153, 154). Consistent with the possible importance of aggregation and trapping, in a humanized mouse study in which a b12-IgA transgene was expressed in hematopoietic stem/progenitor cells, polymeric IgA demonstrated better protection of CD4+ cells than monomeric b12-IgA, and thus established an inhibitory effect of HIV-specific dimeric neutralizing IgA on mucosal transmission of HIV in humanized mice(155).

In order to better resolve the role of IgA and its receptors, further passive transfer experiments are likely to be enlightening, and could leverage protein engineering efforts directed at this subclass. For example, a therapeutic IgA2/IgG hybrid antibody capable of forming J-chain polymers that bind pIgR, activate complement and bind to Fc $\gamma$ RI has been generated(156). A more recent engineering effort produced an “IgGA” capable of binding Fc $\gamma$ RI, Fc $\gamma$ RII, Fc $\alpha$ R and activating complement(157). There appears to be significant opportunity to tune binding to Fc $\alpha$ R through Fc engineering as well as to the less characterized Fc $\alpha$ / $\mu$ R found on follicular dendritic cells, a subset of tonsillar B cells and activated macrophages(158). Additionally, IgA is heavily glycosylated therefore clarifying potential lectin interactions on target or effector or on mucosal surfaces cells could prove valuable. A broader IgA toolkit could be useful for exploring the protective potential of IgA through systemic or mucosal passive immunization studies and gaining insight into compartmental dissemination and effector functions driven by IgA FcRs.

Like the Fc $\gamma$ Rs there are a number of genetic variants including 10 splice variants as well as SNPs in the Fc $\alpha$ R gene and its associated promoter. Three SNPs are found within the promoter, two of which affect promoter activity(159). An SNP within the Fc $\alpha$ R gene leads to an aspartic acid or asparagine in the extracellular domain close to the binding region of IgA though this effect of this is unknown(160). An SNP in the intracellular tail of Fc $\alpha$ R leads to either a serine or glycine at residue 248 and has functional relevance where G248 has significantly more IL-6 release upon IgA crosslinking and is able to retain cytokine release in the absence of the of the common Fc $\gamma$ R-chain. Because the role of Fc $\alpha$ R allotypes in HIV is unknown, evaluation of these genetic markers in relation to HIV protection and disease progression could prove valuable.



## Frontiers in exploiting FcRs for HIV protection and eradication

The development of vectored immuno-prophylaxis (VIP) using andeno-associated virus (AAV) vectors(161) provides the opportunity to circumvent classical vaccination and the expense and logistical challenges of passive immunization with neutralizing antibodies. With VIP, an AAV vector encoding a broadly neutralizing antibody is injected into muscle tissue, which then produces sustained levels of antibody systemically(161). The technology has previously demonstrated sustained protection in rhesus macaques(161) as well as in an Fc $\gamma$ R humanized mouse model(162, 163) and is now in the recruiting stage of a Phase I clinical trial. If proven safe, one could envision applying multi-epitopic antibody cocktails via VIP to capture the breadth and global diversity of HIV and mediate against future virus escape variants. Moreover, programming isotype, subclass and amino acid Fc variants with differential binding to Fc $\gamma$ R, Fc $\alpha$ R, complement, or FcRn into the AAV vector could tune effector function and compartmental distribution for optimal virus protection.

Development of antibodies to move beyond treatment and towards viral elimination from infected individuals are also rapidly progressing(164). The fundamental challenge to strategies to “cure” HIV is the persistence of latent infection in the viral reservoir. Recent studies in rhesus macaque have shown the potential of preventing virus rebound in a fraction of subjects by administering multi-epitopic antibody cocktails with potent virus neutralization(35, 165). AAV technologies may also have a place in virus eradication: in one experiment addressing this possibility, after viral load was suppressed with anti-retroviral therapy a vector encoding a single broadly neutralizing antibody was capable of controlling viremia(166). Studies are underway on how to activate latently infected cells(167, 168) in order to promote their clearance, and a recent study in humanized mice explored a “kick and kill” method of reactivating latent viruses with a mixture of viral inducers in combination with a multi-epitopic antibody mixture and found this strategy could significantly delay rebound of viremia(39). Interestingly, control antibodies with ablated Fc $\gamma$ R binding permitted much more rapid rebound, even when present at a 50 fold higher concentration—again indicating interactions with FcR are a necessary aspect of neutralizing antibody activity *in vivo*.

### Conclusion

Collectively, the studies described here encompass evidence from the setting of natural infection, vaccination, passive transfer, human genetics, and virology to build a strong case as to the role of Fc receptors in the prevention, treatment, and course of HIV infection. As continued efforts to treat and prevent HIV via vaccination and passive transfer of antibody progress, there is strong motivation to pursue optimization of interactions with FcR as a means to enhance anti-viral activity.

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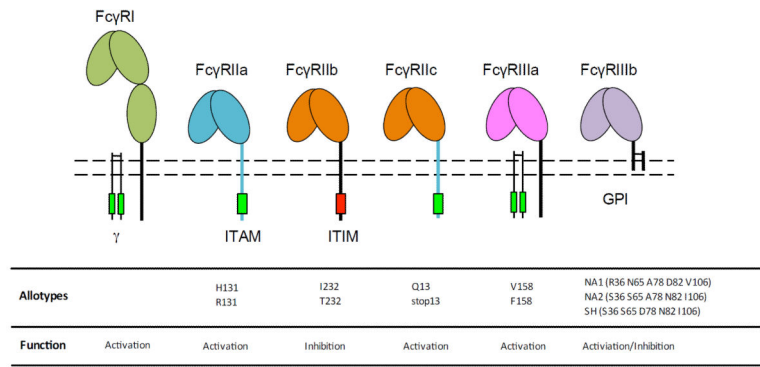


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**Figure 1.**  
FcγR structural and functional characteristics.

**Table 1**  
**Fc $\gamma$ RIIa and Fc $\gamma$ RIIIa alleles and their associations in HIV infection, vaccination and disease progression.**

NE represents allele combinations that were not evaluated.

Observation	HH	HR	RR	VV	VF	FF	Notes	Ref.
Decline in proportion of subjects with CD4+ cells $\geq$ 200/mm <sup>2</sup> over time	-	-	+	-	-	-	RR faster decline	(67)
Decline in proportion of subjects without AIDS over time	-	-	+	-	-	-	RR faster decline	
Risk of <i>P. jiroveci</i> pneumonia as an AIDS-defining illness	+	-	-	-	-	-	HH higher risk, R lower risk	
HIV viral RNA/ml setpoint at ~18 mo	-	-	-	NE	NE	NE	No association	
Monocyte internalization of HIV immune complexes	+++	++	+	NE	NE	NE	HH highest internalization	
Risk of Kaposi's sarcoma	-	-	-	+	-	-	VV higher risk	
Risk of perinatal HIV-1 transmission based on infant allotype	+	-	(+)	NE	NE	NE	HH higher risk, RR lower risk	(68)
Risk of perinatal HIV-1 transmission based on maternal allotype	-	-	-	NE	NE	NE	No association	
Lower HIV replication post vaccination	+	+	-	NE	NE	NE	HH or H/R smaller increase	(69)
Increased risk of infection	-	-	-	+	+	-	V increased risk	(70)
Risk of disease progression	-	-	+	+	-	+	VV and RR/FF increased risk	
Rate of infection for placebo recipients (Vax004)	-	-	-	-	-	-	No association	(71)
Rate of infection for low risk vaccine recipients (Vax004)	-	-	-	+	-	-	VV increased rate	
Risk of infection for vaccine trial participants (Step)	-	-	-	-	-	-	No association	(72)
Risk of infection (RV144)	-	-	-	-	-	-	No association	(73)